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RADIOLOGICAL ACHIEVEMENT 1937–1950

ADVANCES IN CLINICAL RADIOTHERAPY*

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MY TASK in this Symposium is to try to analyze for you the progress made in the everyday practice of radiotherapy. This includes ordinary radium, as we have known it for decades, and roentgen rays, in what is often known as the "deep therapy" range. It will, I think, be generally agreed that each of these makes its greatest contribution as applied to the treatment and cure of malignant disease. There is little doubt that much of the great progress made during these thirteen years stemmed first from developments in Great Britain and from the work of the British School of Radiotherapy.

Out of the welter of trial and error which characterized radiotherapy in the 1920's and early 1930's, we have gradually consolidated our knowledge of the response of the different types of malignant disease until it has become a relatively exact practice. We can now foretell with some certainty which types of tumor can be satisfactorily treated, and which cannot.

MEDICAL ADVANCES

Time permits but the briefest summary of the medical aspects of achievement. Cure by radiation of accessible early squamous cell carcinoma—epithelioma—has been made easier and more certain than cure by surgical excision. This is true of cancer of the mouth, of the uterine cervix, and of most cancers of the skin. It is also true of many other types of cancer perhaps less common, but each providing its quota of cure, and taken together no negligible accomplishment. Of these, cancer of the bladder is probably the most important and the most recently mastered.

This achievement is coupled with a vast improvement in facilities for palliation. In cancer of the pharynx and larynx and of the lung, in cerebral and ovarian tumors, and various others, cure rates are, though rising, still low; but palliative treatment is very valuable. We do not give enough credit to our achievement in the field of deliberate palliation. Because of this power to prolong life and to ease pain, even if not in the end to prevent death, we help to maintain that trust in medicine as one medium through which society shows itself not indifferent to suffering.

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Along with these improvements, achieved only by high dosage, there has been a great diminution of the incidence of necrosis associated with radical radiation therapy. I think there are few people of experience who will not agree that necrosis was the curse of the more empiric period of radiotherapeutic practice, and nearly brought about its downfall. By necrosis I mean true radiation burn, not the normal transient radiation reaction which follows treatment. Necrosis has, to my mind, been almost mastered by the accuracy of modern methods in good centers.

Then there is the great field of surgical collaboration, best exemplified by breast cancer; here, though surgery remains dominant, the radiotherapist has become an indispensable colleague to the breast surgeon. That at least is certain, even though none of us are yet sure how to make our contribution of greatest value.

In the third place, but equally important, there has been the change of policy in the treatment of those growths known to be radiosensitive—the embryonal tumors and the reticulo-endothelial neoplasia. This change—toward the irradiation of much larger volumes of tissue—has augmented the scope of palliation of these diseases when already generalized. It has, however, also brought into the range of curable tumors—provided the growth is still moderately limited in extent—many cases of lymphosarcoma, reticulosarcoma, seminoma testis, Wilms' tumor and medulloblastoma, the last two so common in children.

TECHNICAL ADVANCES

Many factors have contributed to this changed state of affairs, among which several merit special comment here. The first is the increased accuracy of application both of roentgen rays and of radium which makes possible irradiation of minimal volumes of tissue to high dosage in the treatment of squamous cell cancer. For roentgen radiation this accuracy has been achieved by the development of a variety of technical or mechanical processes. These ensure control not only of the direction of the roentgen-ray beam but also of the dose distribution in the whole treated volume. By far the most commonly used are the various "beam direction" devices, several types of which are illustrated in the Scientific Exhibition. Similar principles, in a more elaborate form, are exemplified by schemes of rotation therapy both vertical and horizontal.

Radium technique, too, has progressed very far from the days when radium treatment consisted of little more than the mere insertion into and around a lump of some radium needles, generally those which happened to be in stock or the only stock! Now the pattern of the implant is predetermined, is preceded by careful calculation, and is followed by roentgenographic control and scientific assessment of dosage by the physicist.

The development of surface applicators carrying radium has also been rapid and the modern applicator, still known as a mould, is quite an artistic production and worthy successor to historic Columbia paste.

At this point, let us be clear that these procedures, whether beam direction or accurate radium dose technique, do entail a high degree of painstaking technical work, and the close collaboration for each individual case, of a specially trained physicist. This new profession has become known in Great Britain as "Hospital Physics." Such physicists have now become essential colleagues to the medical radiotherapist.

This elaborate technique is, however, neither more elaborate nor more expensive than the meticulous ritual of the modern surgical operation for cancer. Where the cure of malignant disease is aimed at, it ought to be regarded as equally indispensable. The improvement in the results achieved when compared with the simpler therapy of twenty years ago has been proved to the hilt. There is no excuse for the phrase, so often heard: "But *we* cannot afford that sort of thing." As well might a

surgeon say he cannot afford modern anesthesia, modern chemotherapy, or the highly skilled staff of his operating theater.

RÉSUMÉ

These developments reviewed as a whole can be summarized by saying that we have now learned how to deliver accurately a predetermined dose of radiation to tumor-bearing tissue, whether by roentgen radiation or by radium. It is important to realize that this, in fact, is all we have learned, and that we are, as yet, only ready to begin the next important study, namely the determination of the optimum dose. I use this phrase "optimum dose" in the widest possible sense. In that concept we must include not only the simple idea of quantity of radiation just right for a particular task, but also the determination of the best relationship of that quantity to time. Should the period be long or short? Should dose rate be low or high, increase or diminish? What should be the ideal interval? Then comes their adjustment of these data to individual variation in patient and tumor. There is much yet to learn.

ADVANCES IN ORGANIZATION

Progress can, however, be made in many different directions. Improved organization can produce results just as far reaching as progress in medical principles, in instrumentation or in technique. Over the period under survey, 1937–1950, we in Great Britain have gradually achieved two revolutions in custom and organization. These have contributed equally with scientific developments.

The first is the clear separation of radiology into its component parts—roentgen diagnosis and radiotherapy. In no important medical school in Great Britain are therapy and diagnosis now practiced by the same person. We believe that the knowledge required in each subject is so great that no man can be master of both.

In this context it is of interest to remember the evolution of modern radiotherapy. Roentgen therapy was developed by the general radiologist. Indeed, where diagnosis and therapy are still practiced by one person therapy is all too frequently limited to the use of roentgen rays. In contrast, radium therapy was, for the most part, though not exclusively, developed as a branch of surgery. This may in part explain the lesser emphasis still laid on this valuable agent even in some progressive radiotherapy departments. Modern radiotherapy was created by the fusion of these two and reached maturity only when it was fully recognized that both are equally valuable and must be in the same hands. I remain firmly convinced that this decisive splitting off of radiotherapy, so characteristic of British practice of today, has been in itself a major achievement, which has yielded substantial dividends in mature development of that specialty.

The second characteristic change affects the administration of this new specialty of radiotherapy itself, which will now be concerned not only with radium and roentgen rays, but also, in this new era with radioactive isotopes, neutrons and megavolt therapy. The small scale therapy center handling less than some 500 cases of cancer per annum is gradually being eliminated. The resultant centralization permits not only medical specialization but also collects in one center enough patients to allow full use of the varied and expensive instruments and of the many technical skills required. The last of these, technical skill, is of great importance and calls for an integrated team not only medical but with its pathologists, physicists, mould room technicians, therapy radiographers, the records officer and the electrical engineer. Only where substantial numbers are handled is it possible to keep these essential workers fully employed. Yet each of them is a big factor in the ultimate aim of obtaining the greatest possible number of cures.

Centralization is thus in itself an achievement of great value. It therefore seems desirable to examine its main characteristics. In the first place, it should be noted that the incidence of malignant disease is

remarkably constant. Knowing the minimum number of patients required to maintain an effective unit, we can in practice express this in terms of population. The minimum unit so required is of the order of one million, but efficiency can increase with centralization of all the work from considerably larger units of population. In the new British Health Service this has usually entailed the provision of one radiotherapy organization for each hospital "region." In many other countries the social structure is such that one dominant city serves as center for a population unit of one to two or three million, as is illustrated by the Provinces of Canada or of the States of Australia. Again one single major radiotherapy center in this dominant town, with feeder clinic services in the surrounding area, makes for greatest efficiency. In the closer knit industrial areas of the world, the desirability of a single center for one area is less obvious, but it remains essential somehow to reduce the total number of treatment centers until each is dealing with substantial numbers of patients.

This plan makes not only for medical efficiency, but has financial advantages, too, because it makes greatest use of plant and equipment, often extremely expensive, and also greatest use of medical experience which is as yet rare and hard to acquire. Lastly, this is the only way in which the prospective specialist in this new field of work can gain enough experience in a reasonable time. It is therefore essential for teaching.

TABLE I

RESULTS OF TREATMENT OF CANCER OF THE CERVIX UTERI

As Shown in "Heyman's" Reports—Summated Figures for 17 Hospitals

	Number Treated	Five Year Crude Survival
Before 1936	15,560	30%
1936–1941	12,343	37%

Hospitals reported

3 United States
4 Great Britain
5 Scandinavia
5 Other North European

EVALUATION OF RECENT ADVANCES

One may well ask—Is there any way to get objective measure of the results of these changes on the general pattern of medicine? I believe we can get some tangible evidence that radiotherapy has made an increasing contribution.

The most direct evidence would clearly be a rising cure rate shown on an extensive scale, either nationally or internationally. Unfortunately, few such statistics yet exist. One crisp example on a world wide basis, however, we do owe to Heyman's indefatigable genius. The over-all results of cancer of the cervix treated by radiotherapy, as shown in Heyman's latest report, are compared in Table I with the results given in the earlier reports. The percentages given are the crude survival rates summated from the same seventeen hospitals which featured in both of the reports—an improvement from 30 per cent to 37 per cent over-all in somewhat over a decade.

I know of no other world-wide surveys such as this. Study of reports, however, from single centers for individual diseases over the last twenty years cannot fail to

TABLE II

RESULTS OF TREATMENT OF CANCER OF THE MOUTH

Holt Radium Institute, Manchester

All Cases Treated Radically either by Radium or Roentgen Therapy

Years	Number Treated	Five Year Net Survival
1928–30	422	24%
1931–33	525	32%
1934–36	532	29%
1937–39	387	34%
1940–42	486	37%
1943–45	506	40%

convince the unbiassed observer that there has been steady improvement. I would like to illustrate this by some results of treatment of cancer of the mouth from the Radium Institute in Manchester over the last twenty years. Table II shows for a sequence of three year periods the net survival rate for all cases of cancer of the mouth treated radically. The cure rate is clearly rising. Even the temporary drop to 29 per cent is evidence of interest as representing a short trial of an unsatisfactory technique later corrected with the results shown.

Survival rates are, however, not the only available evidence of progress. There are other significant facts worth analysis. The first is the contrast between the number of cases of cancer treated by surgery and those treated by radiotherapy. At the present time we are all of us, even radiotherapists, too apt to think of surgery as the major contributor to the cure of cancer, with radiotherapy giving valuable but supplementary aid. However, as Table III shows for British practice, when the two are assessed in terms of total patients treated, modern radiotherapy is found to be the major partner in the alliance. The two columns in the table show, for a typical sample including regional surveys and university hospitals and other hospitals, the percentage of all treated cases treated by each agent. Column one shows total radiotherapy, column two total surgery. Cases treated by both methods are shown in column three, but are also included in each of the first two columns so that their percentages summated exceed 100. Because of the extensive use of radiotherapy for palliation it is more difficult to determine which yields greater returns in terms of cure. In one of the regional surveys included in the table an attempt was also made to assess this. It was there shown that for the total cases treated primarily by radiotherapy not only was the percentage surviving five years greater but the actual number surviving five years was greater than from surgery. I believe that this is, in fact, a true evaluation of modern radiotherapy.

Table III

THE RATIO BETWEEN THE NUMBER OF CANCER CASES TREATED: (A) BY RADIOTHERAPY; (B) BY SURGERY

	Total Treated Cases		Surgery plus Radiotherapy (Included in *each* of the previous columns)
	Treated by Radiotherapy	Treated by Surgery	
An English Regional Survey	62%	49%	11%
A Scottish Regional Survey	67%	59%	26%
An English University Hospital	67%	61%	28%
A Scottish University Hospital	70%	42%	12%
An English General Hospital	75%	47%	22%
A "Cancer" Hospital	80%	37%	17%
A London University Hospital	87%	46%	14%

I deliberately say modern radiotherapy, because the other striking piece of evidence is drawn from observation of the growth in numbers of cases seeking assistance, which is found wherever successful radiotherapy is practiced. Where a thing is good and it works, the profession uses it and its use grows. Such growth is, then, of itself evidence that it is valuable. Where a thing is only a fashion and has no solid basis of success, it may have a vogue for a period—fashions do—but it does not endure.

Table IV shows the actual numbers of cancer cases seeking help, which were registered in the years 1933, 1938, 1943 and 1948 in representative English radio-

therapy centers. Nothing can be more convincing of the increased acceptance by our colleagues, despite individual opposition, of radiotherapy as an exact science which has made real contribution to the cure of some types of malignant disease. All the centers reviewed tell the same story of rapid expansion and increasing demand.

So far, I have been speaking of the radiotherapy of today—ordinary radium and deep roentgen therapy. We have seen great advances in reliable knowledge of the relative sensitivity of the different types of tumor. We have seen spectacular improvement in the accuracy both of measurement and of administration of radiation. We have seen that achievement has foundations not only in technical knowledge, but in changes of organization. The greatest of these have been the establishment of radiotherapy as a speciality in its own right and its centralization on an extensive scale.

Every one of these things will be equally essential to the effective application of all the newer radiation agents, including super-voltage therapy and isotopes, about which we shall hear much in the various symposia of this Congress.

Moreover, it should never be forgotten that the achievement made in the use of the older agents remains with us. The newer weapons will, we hope, not only improve our work in the field already partly mastered, but may well break new ground and bring yet other types of malignant disease into control in the next thirteen years.

TABLE IV

GROWTH IN DEMAND FOR RADIOTHERAPY

Increase in England in the Numbers of Patients with Malignant Disease Sent to Radiotherapy Centers for treatment

Year	1933	1938	1943	1948
Provinces:				
A "Cancer" Hospital	1,377	1,965	3,539	4,400
University Hospitals:				
Region A	163	577	1,012	1,638
Region B	350	630	970	1,620
Region C	367	820	832	1,630
Region D	522	1,058	1,141	1,322
A General Hospital	316	414	637	861
London:				
A "Cancer" Hospital	712	801	677	1,306
A University Hospital	440	738	997	1,300

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ROENTGENOLOGICAL AND PATHOLOGICAL OBSERVATIONS IN ANTIGENIC PNEUMONITIS

ITS RELATIONSHIP TO THE COLLAGEN DISEASES*

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IN THE past we have been accustomed to think of disease processes as originating in the pathological or functional derangements of definite organs as, for example, "cirrhosis of the liver," "tuberculosis of the lung" or "ulcer of the stomach." We think of alterations in the blood or lymph as reflections of disease of the bone marrow or lymphatic structures, not as disease states of the blood plasma or lymph itself. We cannot conceive of anything but temporary derangements of the fluids and other non-structural elements of the body. The intercellular collagenous structure is taken for granted as a medium by which the cellular structures are maintained in proper relationship; in other words, it serves as a filler between the cellular elements of the body. Observation by clinicians would indicate that derangement of this intercellular substance may be an important common factor in the development of certain conditions known as "collagen diseases." The conditions most commonly identified with this group are as follows:

Hypersensitive states resulting in sensitization reactions to foreign protein; serum reaction.

Drug sensitization, possibly by combination of sensitizing agent with albumin inside (or outside) the body.

Blood incompatability in transfusions.

Acute glomerulonephritis (with azotemic edema).

Periarteritis nodosa, resulting in reaction, centered more particularly about blood vessels.

Rheumatic pneumonitis, in which transitory joint involvement is a prominent feature.

Rheumatoid arthritis, proliferation of synovial membrane of joints.

Disseminated lupus erythematosus, associated especially with butterfly skin lesions on nose, cheeks, and involvement of serous membranes, pericardial, endocardial, pleural, and abdominal.

Dermatomyositis.

Scleroderma.

Steinberg has summarized briefly some of the pertinent facts concerning our knowledge of connective tissue:

Connective tissue is composed of two essential elements: (a) fibrillar material, and (b) interfibrillar substance.

(a) These fibrils under electron microscopic examination show cross-striations of regular periodicity (646 Å); they divide like the branches of a tree. These fibrous elements are composed of collagen reticulin and elastic fibers; they are proteins of high molecular weight. Collagen, when heated in aqueous solution, becomes amorphous gelatin. "Embryonic collagen fibers are soluble in salt-free dilute acid and when these solutions are treated with salt or neutralized, the proteins precipitate as fibers which possess the same fine structure as the native fibers."

(b) The interfibrillar substance in turn is composed of at least two components: (1) an amorphous ground substance, and (2) a cement substance. Little is known of the chemistry of the amorphous ground substance.

The cement substance proper serves as a bed for the fibrous elements. It contains protein and mucopolysaccharides. There are four known mucopolysaccharides. Of these, hyaluronic acid is best known. This

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acid is hydrolyzed by a specific enzyme, hyaluronidase, known as the "spreading factor" in streptococcus and other infections which contain this enzyme. It has been suggested that this action is produced by effect on the cement substance. Observations by clinicians would seem to indicate the possible involvement of this collagenous material as the basis of the pathological process in a number of conditions known as "collagen diseases."

These widely differing groups of diseases would seem, on first consideration, to have little to identify them with a common etiology. They have been observed on so many occasions to develop similar signs and symptoms during the course of the disease, however, that the possibility of a common etiological factor must be considered (Kampmeier). Each has some predominant clinical or pathological characteristic by which it can be identified, such as manifestations of foreign protein reaction; in hypersensitive states, in drug sensitization and in blood transfusions with incompatible blood; anuria and azotemic edema in glomerulonephritis; periarterial proliferation with resulting high blood pressure in periarteritis nodosa; multiple joint manifestations and certain characteristic pathological cell formations in rheumtatic pneumonitis; butterfly skin reaction on nose and face in lupus, together with occurrence of certain characteristic cells known as lupus erythematosus cells.

Yet, in all, there is an associated common fundamental pathological lung reaction which seems to establish a common denominator for all of these diseases. The widely divergent clinical manifestations of these diseases would indicate that any such common etiological factor might lie in the involvement of a common structure such as the connective tissue (Banks).

The purpose of this paper, then, will be to endeavor, by correlation of roentgenological and pathological findings, to throw some light on the nature and character of these diseases.

The collagenous connective tissue is an all pervading substance present in all tissues throughout the body. It would be reasonable to suppose that any disease process affecting this structure would manifest itself in the lung as well as in the other organs and structures of the body, and that possibly these changes might be observed by roentgen examination of the lungs. Let us, then, utilize the lungs as a roentgen window for observation of any pathological process which may be going on in the body.

One of the most common types of anaphylactic reaction is that due to sensitization to horse serum. Such cases are usually mild, being accompanied by urticarial reaction, eosinophilia, constitutional reac-

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Fig. A. Sulfa drug sensitivity. Pathologic alterations noted in a case of sulfa drug sensitivity. Septal swelling, hyaline membrane, prominent mononuclear cell infiltration within alveolar walls. (Hematoxylin and eosin, ×340)

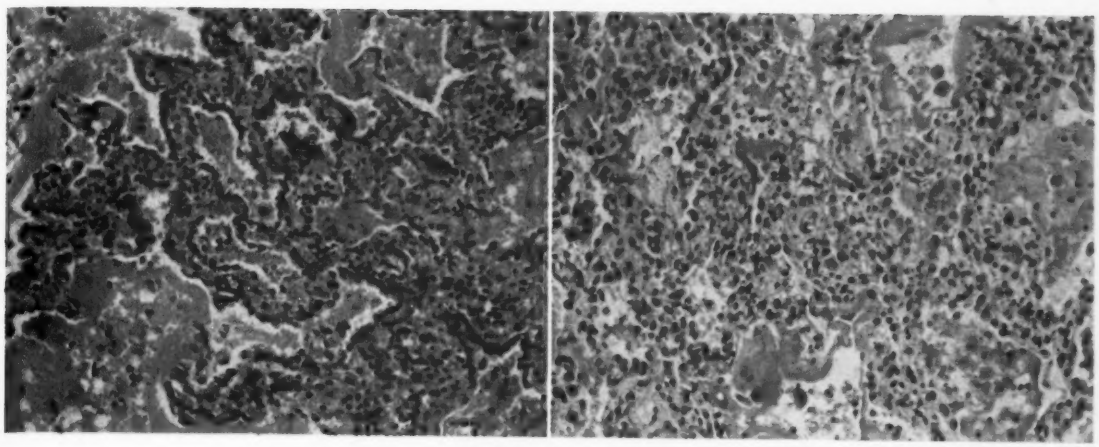
Fig. B. Glomerulonephritis subsequent to sensitizing transfusions, the lung showing intense septal thickening and heavy mononuclear infiltration. Dense membrane lining alveoli prominent—capillary damage indicated by numerous hemosiderin-laden macrophages. (Hematoxylin and eosin, ×380)

Fig. C. Lung in periarteritis nodosa showing intense widespread hyaline membrane plastered against septal wall. Mononuclear cells in thickened septae. (Hematoxylin and eosin, ×310)

Fig. D. Rheumatic lung. Lung shows considerable septal thickening, with prominent lymphocytic infiltrate. Characteristic findings of "Masson granulomas" are a noteworthy feature. Hyaline membrane occurs in rheumatic lung but not of the same intensity. (Hematoxylin and eosin, ×310)

Fig. E. Disseminated lupus erythematosus. Mononuclear cells present in alveolar walls. Hyaline edema membrane filling alveoli associated with fresh hemosiderin-laden macrophages. Findings encountered in lung of lupus erythematosus. (Hematoxylin and eosin, ×310)

Fig. F. Scleroderma. Dense fibroblastic and collagenic scar in the lung from a case of scleroderma. Septal wall thickening present. The process is much older; the acute manifestations such as hyaline membrane and mononuclear infiltration are not prominent. (Hematoxylin and eosin, ×310)



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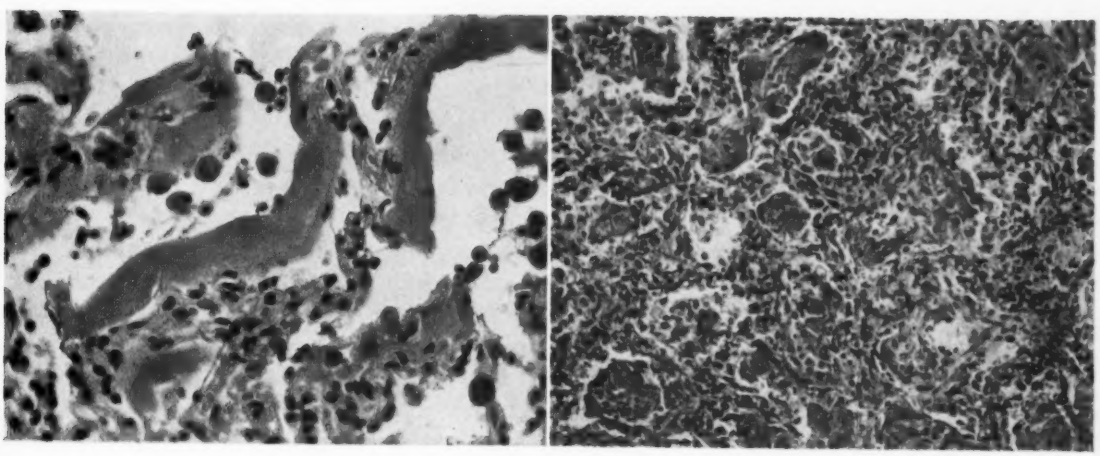

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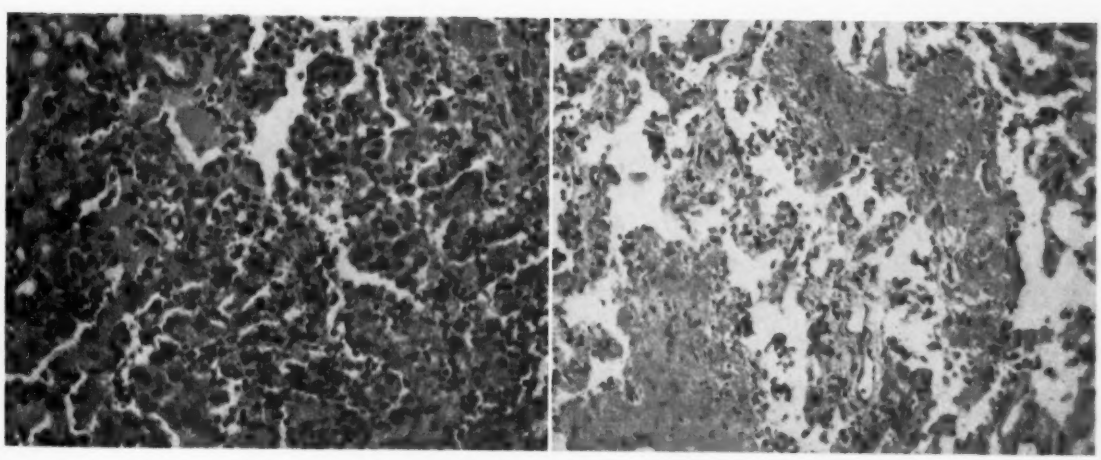

E F

tion, etc., rarely causing death. Few autopsies, therefore, are available. Such mild cases show little, if any, roentgen manifestations in the lungs since the dose is so small and the reaction so mild.

Occasionally, however, the reaction to such agents is prompt and severe, coming on immediately and causing death within a few hours to a few days. Similar anaphylactic reaction occurs from drug sensitization and from blood transfusions with incompatible blood. These amount to essentially the same circumstances; the injected material constitutes a foreign protein to which the body is sensitive (Rich, and Longcope and Winkenwerder).

In such cases the lung fields may rapidly assume the characteristic picture of so-called azotemic edema. The hilar regions and inner zones of the lungs present dense, blotchy areas of increased density similar to that seen in pulmonary edema, radiating outward toward the periphery of the lungs, but stopping short of the outer edges, leaving clear peripheral zones. The picture differs from that produced by acute pulmonary edema from cardiac failure in that it stops abruptly before it reaches the outer margins of the lung, and it is not associated with enlargement of the cardiac shadow which would be expected in such cases. Furthermore, the shadow may vary from the blotchy appearance of edema described above to one of heavy linear markings radiating outward from the hilus like a sunburst, but in no case extending into the peripheral zones, the exact location in which one would expect the greatest amount of edema. This, then, is the form of edema which previous experience has indicated is associated with some form of nephrosis—so-called "azotemic edema." Ordinary congestion and edema of the lungs from cardiac failure fills the entire lung structures, especially in their bases. Just why pulmonary edema should assume another form under certain circumstances has not yet been satisfactorily explained. Edema of the lungs associated with chronic cardionephritis does not assume this form.

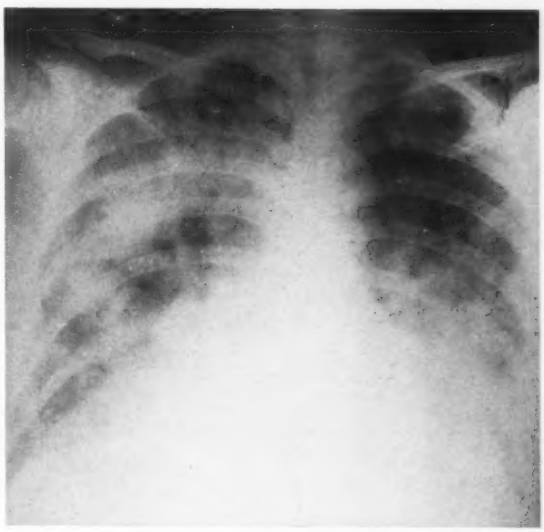

Fig. 1. Case 1. Drug sensitization developing after repeated doses of sulfadiazine with glomerulonephritis and azotemic edema.

In children, chronic nephrosis may exist for years with high non-protein nitrogen, causing renal rickets with gross deformities in bone growth, and yet edema of the lungs may not develop at all until just before death, and this is never of the azotemic type. Rendich, Levy and Cove, in their excellent article on azotemia, point out that this relatively rare form of pulmonary edema is not present in all instances in which the nitrogenous products are greatest in the blood.

In the case of acute glomerulonephritis, without the influence of any sensitizing agent, a similar pulmonary reaction may occur, although the immediate cause may not be evident and the mechanism may be somewhat different.

Drug Sensitization with Development of Antigenic (Azotemic) Pulmonary Edema.

Case 1 (Fig. 1). F. S., white female, aged fifty-five, entered St. Mary's Hospital on May 8, 1944, severely ill with temperature of 99.4° to 101° F., dyspnea, cough, nausea, epigastric pain, ankle edema and skin eruption.

Past History. Treated with sulfadiazine five weeks ago for upper respiratory infection—without reaction. Developed pneumonia.

Treated again with sulfadiazine three weeks

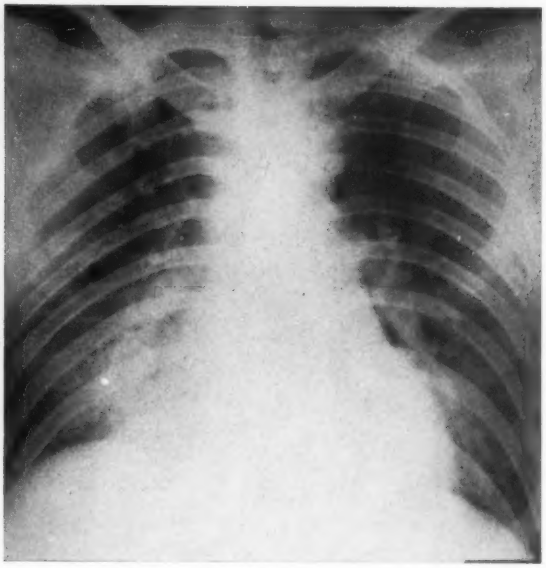

Fig. 2. Case II. Drug sensitization resulting in anaphylactic shock with antigenic (azotemic) edema of the lungs. Similar reaction may result from any other foreign protein such as horse serum.

later, followed by severe sensitization reaction with erythematous skin rash on face, neck, chest and extremities.

Two days before entrance into the hospital she became suddenly dyspneic, with severe epigastric pain and general edema. Large, blotchy type hemorrhagic areas developed over body. Died five days later.

Physical Examination. Coarse rales in chest. Heart normal in size, normal function. Liver, spleen and kidneys not palpable. Extremities edematous, cold and white.

Laboratory Findings. Electrocardiogram showed sinus tachycardia.

Urinalysis: Specific gravity 1.017, albumin 3 plus, sugar 1 plus, leukocytes 3 to 5, erythrocytes 5 to 7 per high power field.

Blood: Leukocyte count 68,150; differential count, juvenile cells 8 per cent, stab forms 21 per cent, segmental forms 64 per cent, lymphocytes 2 per cent, Kahn test 4 plus.

Roentgen Examination. This examination revealed azotemic edema of the lungs of an extreme degree, showing pronounced edema in the central structures and preservation of a clear peripheral zone. This persisted for several days, gradually subsiding and resuming normal aeration.

Diagnosis. Acute sulfa drug sensitization; antigenic (azotemic) pulmonary edema; syphilis; myelogenous leukemia.

Anaphylactic Shock from Drug Sensitization with Antigenic (Azotemic) Edema of the Lungs. Similar to other types of foreign protein reaction such as that from horse serum.

Case II (Fig. 2). K. E., white male, aged twenty-four, entered the hospital with history of taking sulfadiazine for gonorrheal infection two days previously. An acute anaphylactic reaction followed, with complete suppression of urine. Roentgen examination of the chest taken on entrance to St. Mary's Hospital showed edema of the lungs which assumed a characteristic form. Patient died three days after taking the drug.

Pathological Examination. As the emphasis in this contribution is upon the alterations in the lung, the pathologic description will be restricted to a brief description of the lesions in these organs. The lungs weighed 1,020 and 1,850 grams, with marked edema, and a great deal of fluid was expressed from the cut surface. The fluid exudate in the alveoli appeared to have a gelatinous nature. The striking feature, on microscopic examination, was the widespread involvement of the lungs, with a dense hyalin membrane plastered to the septal walls. The cells, both within the septa and also in the alveoli, were mononuclear in type. No bacteria could be demonstrated by staining methods.

The other viscera, heart, liver and kidneys, showed obvious evidence of allergic lesions, indicated by fibrinoid necrosis of small vessels and interstitial granulomatosis.

Transfusion with Incompatible Blood Causing Acute Glomerulonephritis with Antigenic (Azotemic) Pulmonary Edema.

Case III (Fig. 3). B. H., white female, aged seventeen. Patient was perfectly well until one year ago, August, 1948, at which time she aborted a two months' fetus. Following this she became very anemic. She recovered after a three months' course of liver extract and iron to build up her blood.

In March, 1949, she became pregnant again, developed nausea and vomiting, but no bleeding.

On July 1, 1949, she was admitted to the Deaconess Hospital because of anemia, and pain in the right lower quadrant of the abdomen. At this time the erythrocyte count was 1.16 million; hemoglobin 3 gm.; leukocyte count

9,500; Kahn test negative; blood type: group A, Rh negative. Urine: albumin 2 plus, sugar negative. Received four blood transfusions without any reaction and was improved. Responded well and was discharged.

About August 1, 1949 (three weeks before admission to St. Mary's Hospital), the patient noticed blood in the urine and swelling of extremities and face. Admitted to St. Mary's Hospital, August 26, 1949, because of "severe, constant substernal pain aggravated on deep breathing; does not radiate. Slight non-productive cough and dyspnea."

Physical Examination. Well developed and nourished white female, aged eighteen. Pale and puffy about face. Lungs: Few fine crepitant rales left base (dependent), otherwise negative. Extremities: Pitting edema but no petechiae.

Roentgen Examination, August 28, 1949, revealed typical antigenic (azotemic) edema of a pronounced degree, showing clearly the central radiations and peripheral clear zones.

Laboratory Findings.

Urinalysis: Albumin 2 plus, erythrocytes 1 to 4 and leukocytes 10 to 15 per high power field, no casts.

Blood: Erythrocyte count 1.07 million, hemoglobin 3.9 gm., leukocyte count 13,950, with a normal differential count. Reticulocyte count 6 per cent. Proteins 5.46 gm. per cent, albumin 3.25 gm. per cent, globulin 2.21 gm. per cent, nonprotein nitrogen 35 mg. per cent, CO_2 combining power 16.7 millimoles per liter, chloride 10 milliequivalents per 100 cc., Kahn test negative.

Bone marrow: Nucleated cell count 56,000.

August 26, 1949: On admission, 1,000 cc. banked blood given.

August 27, 1949: Second blood transfusion, 1,000 cc. Continuous inspection and checks for gross blood in urine negative.

August 27, 1949: Third blood transfusion, 1,000 cc.

August 28, 1949: Still intermittent precordial pain. Urine grossly bloody. Dyspnea. Respirations 44 per minute. Temperature 99.2° F.

August 29, 1949: Blood transfusion, 500 cc. concentrated cells. Substernal pain. Urine grossly bloody. Blood pressure 130/80.

August 30, 1949: Plasma, 500 cc. plus 500 cc. concentrated cells given. Crepitant rales both bases. Gross hematuria. Temperature ranged between 102.6° and 103.4° F. Pulse 160 per minute. Respirations 55 per minute. Blood pressure 145/55.

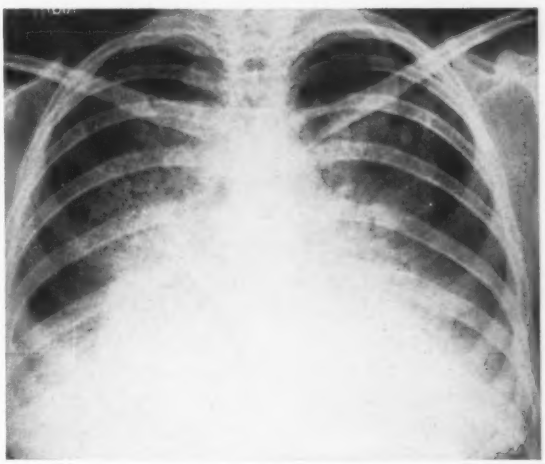

Fig. 3. Case III. Transfusion with incompatible blood instigating acute glomerulonephritis with antigenic (azotemic) pulmonary edema.

August 31, 1949: Labor pains with spontaneous delivery. Twelve noon, patient died.

Pathological Examination. In this instance, the lungs were the viscera showing pivotal pathology. The lungs each weighed over 1,000 grams and were dark brown in color and meaty in consistency. This textural change extended out to the pleural borders.

Microscopically, the involvement of the lungs was generalized. The histopathologic appearance was startling with widespread interstitial mononuclear infiltration intimately associated with sweeping bands of hyalin membrane. Incorporated into the hyalin membranes were hemosiderin-laden macrophages; in some regions the hyalin membrane gave a positive hemoglobin stain indicative of the briskness of the reaction, presumably the hemoglobin derived from liberated cells from damaged capillaries due to the profound vessel injury of an allergic nature. Basophilic macrophages were festooned along the septal linings and the occasional "Masson body: bourgrons conjunctif" was noted.

It was contended that the widespread lung involvement of such a nature could best be described as an "allergic pneumonitis." The presence of an acute glomerulonephritis of the same age as the lung lesions was further evidence supporting the belief that the tissue changes were the morphological reflection of antigen-antibody conflict. The administration of whole blood in previously sensitized persons may give rise to clinically dire results on occasion. Clinically, it is known that it can be dangerous

to give antigenic substances to individuals who possess an allergic background such as rheumatic fever, disseminated lupus and possibly allied conditions.

Acute Glomerulonephritis (Adult) of Less Severe Degree without Demonstrable Cause, with Recovery.

Case iv (Fig. 4, *A* and *B*). C. S., admitted to the St. Louis City Hospital on February 24, 1946, with a history of two weeks' periorbital swelling, progressing to puffiness of entire face and later of the entire body.

There was no history of recent serum or drug injections, or medication of any sort; no recent illness.

Just prior to admission the patient developed shortness of breath, but on physical examination the lungs seemed clear although general anasarca was present.

Roentgen examination of the chest showed the typical picture of antigenic (azotemic) edema, with bilateral densities surrounding the hilar regions and clear peripheral lung zones.

Blood pressure 175/40.

Laboratory Findings. Urine showed red blood cells, casts and albumin. Non-protein nitrogen 35 to 45 mg. per cent.

Bed rest, diet and sedation were prescribed and the patient recovered and was discharged in one month.

Patient was readmitted to the hospital almost two years later for a stab wound of the chest. His lungs remained normal, and there was no evidence of kidney involvement at this time.

Acute Glomerulonephritis (Child) Following Exposure to Cold.

Case v (Fig. 5, *A* and *B*). D. D., white female child, aged four and one-half, admitted to St. Mary's Hospital on April 14, 1949, with a history of recurrent attacks of puffiness and edema of face, neck and extremities whenever she was exposed to cold or rainy weather during the past few winter months.

Past History. Not significant.

Present Illness. As above; otherwise negative.

Physical Examination. On entrance patient showed extreme swelling of face, abdomen and extremities. No other indication of abnormality. Very lethargic. Temperature 101° F.

Laboratory Findings.

Urinalysis: Albumin 2 plus to 4 plus, erythrocytes 8 to 10 and leukocytes 4 to 6 per high power field.

Blood: Erythrocyte count 3.65 million, non-protein nitrogen 43 mg. per cent.

Roentgen Examination. Typical antigenic (azotemic) edema of the lungs with dense shadows about the hilar regions, extending outward into both lung fields but stopping short of the periphery, leaving clear zones at the outer margins of the lungs. The cardiac shadow appeared normal. Re-examination ten days later revealed complete clearing of the lungs.

In periarteritis nodosa a similar pulmonary

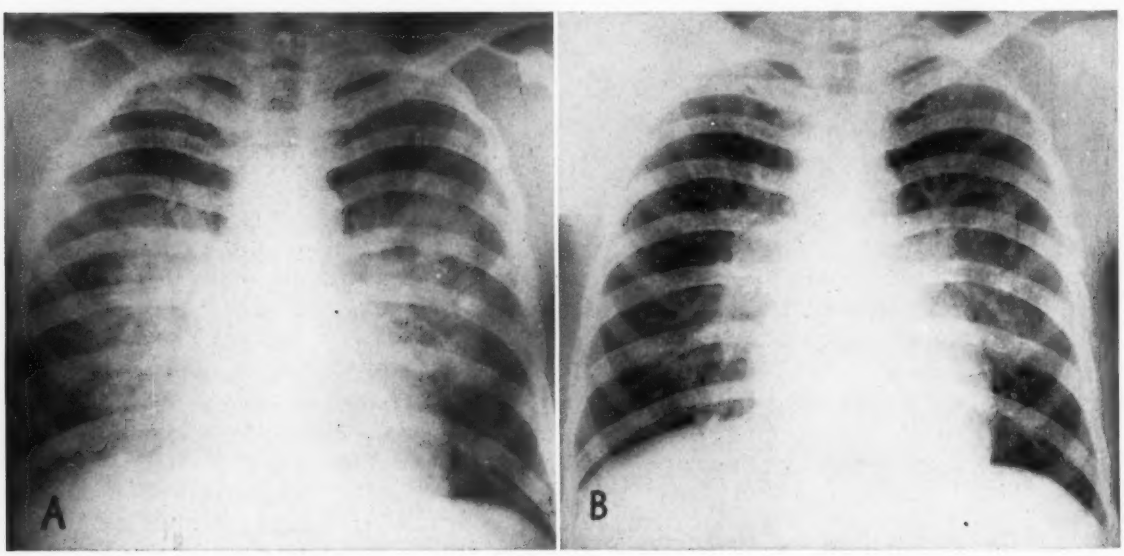

Fig. 4. Case iv. (*A*) Acute glomerulonephritis, of a less severe degree, in an adult without demonstrable cause—with recovery. (*B*) Complete absorption of edema in four days with restoration to normal.

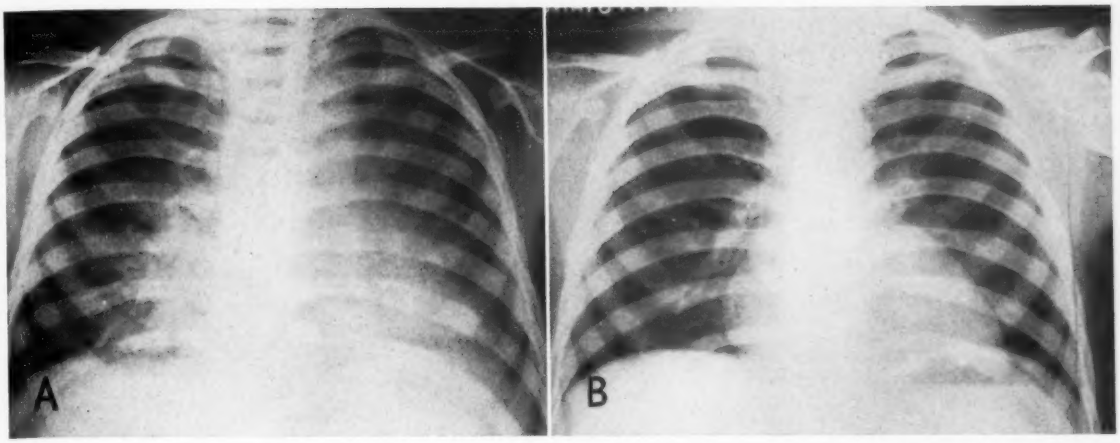

Fig. 5. Case v. (*A*) Acute glomerulonephritis in a child following exposure to cold—recovery. (*B*) Recovery in two weeks with absorption of edema.

reaction may occur; it is usually instituted by an acute allergic reaction to foreign protein such as horse serum (Rich). The acute reaction subsides only to be followed by progressive primary changes in the walls of the blood vessels, giving rise to a variety of symptoms depending on the regions most predominantly involved. Microscopic examination of the vascular structure reveals involvement of the vascular wall and perivascular tissues by an inflammatory reaction which ultimately may cause weakening of the vessel walls with multiple small aneurysm formations and infarcts. Proliferation of the vascular walls results in narrowing of the lumen, high blood pressure and all of its complications and sequelae. While the greatest damage is probably done during the acute stage of the anaphylactic reaction, and death may result in a few weeks, still there is evidence to indicate that sometimes the patient may survive the original anaphylactic reaction and the sensitizing agent may continue causing the process of vascular proliferation under the influence of its persistent action. There is further evidence in the occasional recovery of such patients, indicating that it is possible for such antigenic agents to be overcome by the body and other effects eliminated (Klein).

Periarteritis Nodosa Following Acute Pneumonitis Not Unlike Azotemic Sensitization Reaction.

Case vi (Fig. 6). E. A., white male, aged sixty-seven, entered St. Mary's Hospital on February 23, 1948.

Past History. Not significant.

Present Illness. Patient was perfectly well until February 16, 1948, when he was awakened in the morning with severe pain in the right lower chest intensified on deep inspiration. There was severe pain, fever as high as 103° F., and night sweats. Pain, night sweats and fever persisted, and on the day of entrance into the hospital, about a week later, a cough with "whitish" expectoration had developed. This later became mucopurulent.

Physical Examination. Chest, lungs: No dullness, breath sounds vesicular, possible friction rub. Heart: Rate 120 per minute, regular, slightly enlarged, otherwise negative. Blood pressure 160/90.

Laboratory Findings. Urinalysis negative.

Blood: Erythrocyte count 4.50 million, hemoglobin 14 gm., leukocyte count 10,400,

Fig. 6. Case vi. Periarteritis nodosa following acute pneumonitis not unlike azotemic edema. It is believed that the periarterial reaction is a manifestation of continued reaction to a sensitizing agent which still remains after the initial reaction has subsided.

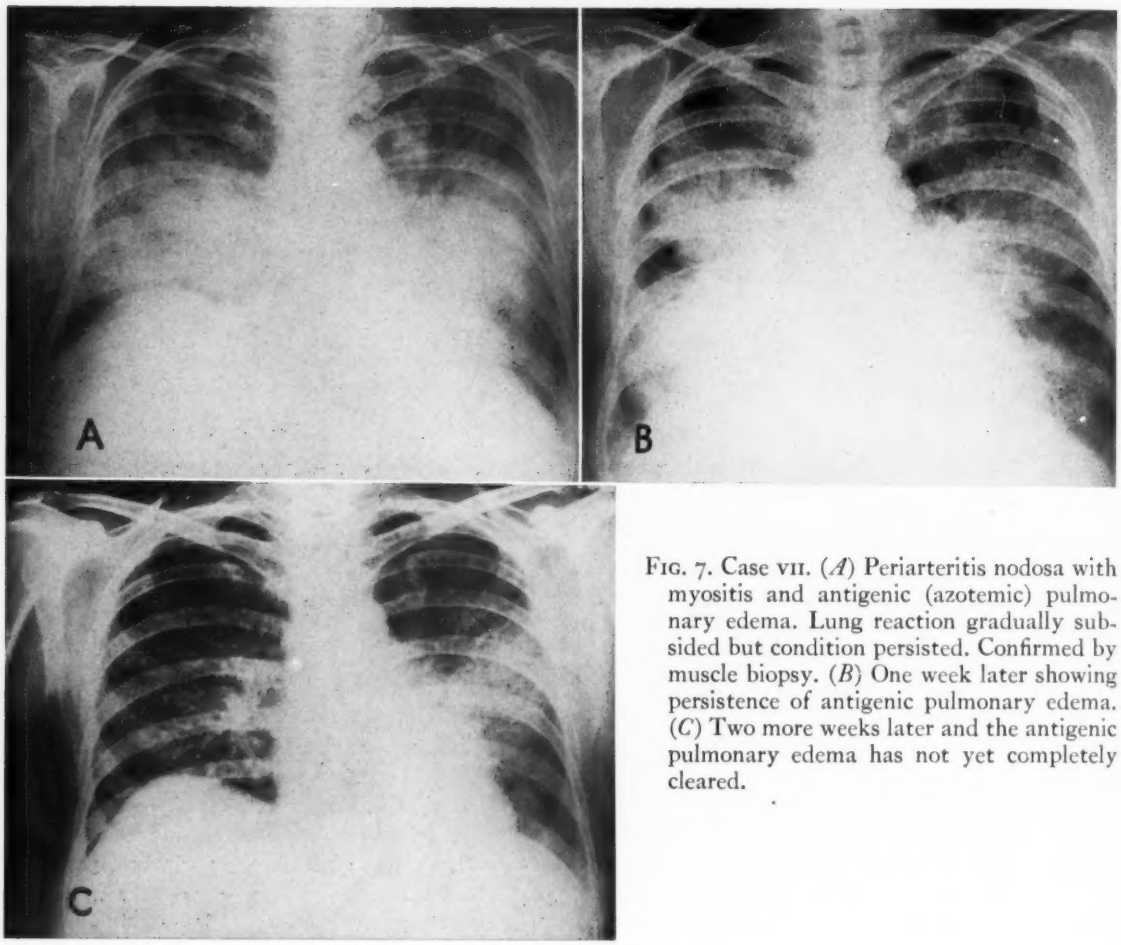

Fig. 7. Case vii. (*A*) Periarteritis nodosa with myositis and antigenic (azotemic) pulmonary edema. Lung reaction gradually subsided but condition persisted. Confirmed by muscle biopsy. (*B*) One week later showing persistence of antigenic pulmonary edema. (*C*) Two more weeks later and the antigenic pulmonary edema has not yet completely cleared.

blood sugar 90 mg. per cent, non-protein nitrogen 37 mg. per cent, Kahn test negative. Differential count (Schilling): juveniles 2 per cent, stab forms 5 per cent, segmental forms 74 per cent, lymphocytes 14 per cent, eosinophils 3 per cent and monocytes 1 per cent.

Roentgen examination of chest made on admission showed areas of increased density about both hilar regions and in the bases of both lungs, not unlike azotemic edema. No specific infiltration or consolidation could be seen. There was thickening of the interlobar pleura on the right side, but no demonstrable pleural effusion. The cardiac shadows were slightly enlarged, but all normal cardiac curves were well preserved. The aortic shadow was broadened and irregular.

Electrocardiogram showed sinus arrhythmia and tachycardia.

Death within three weeks, with postmortem findings of periarteritis nodosa and multiple infarcts of kidneys, spleen and other organs.

Comment. There was no demonstrable allergic etiology and no abnormal urinary findings at the time the chest roentgenogram showed greatest involvement. Albuminuria 2 plus later on. Non-protein nitrogen was 37 mg. per cent at the time of lung findings, going to 75 mg. per cent later. The lung fields had cleared by the time the urine and blood findings had become positive.

Periarteritis Nodosa with Myositis and Antigenic (Azotemic) Pulmonary Edema.

Case vii (Fig. 7, *A*, *B* and *C*). B. B., white female, aged sixty-two, entered Firmin Desloge Hospital on April 17, 1950, because of chronic cough and hemoptysis.

Past History. Dry cough of six months' duration, with loss of 50 pounds in weight. Admitted to St. Louis City Hospital in December, 1949, for bronchoscopy which proved to be negative.

Roentgen examination at that time failed to reveal any significant pathology. A persistent eosinophilia was noted, however.

Present Illness. Entered Firmin Desloge Hospital because of severe cough and hemoptysis, dyspnea and extreme weight loss. Oxygen administration was necessary on admission.

Physical Examination. Chest, limited expansion bilaterally, dullness to percussion midscapular area to apex, moist rales in bases.

Roentgen examination of chest on entry, April 18, 1950, revealed findings of extreme azotemic pneumonitis with dense markings in hilar regions radiating outward into both lung fields but leaving a clear peripheral zone. The cardiac shadow was not unusually enlarged and there was no definite evidence of effusion.

Laboratory Findings. On entry, non-protein nitrogen was 67 mg. per cent. It dropped to 50 mg. per cent on May 9, and again mounted to 86 on May 12 and to 100 on May 15, where it remained until the patient's death.

Urinalysis was negative on entry, with development of some albuminuria later.

Electrocardiogram showed sinus tachycardia.

Cystoscopic examination revealed fibrous obstruction band at urethrovesical junction; diverticula of bladder and some cystitis. Purpuric areas on legs.

Biopsy of the gastrocnemius muscle showed periarteritis nodosa and myositis.

Blood: Leukocytes 6,650 on admission, rising to 20,000 the day before death. Erythrocytes and hemoglobin were low until built up by repeated transfusions. There was persistent eosinophilia of 29,000 throughout her illness which never could be accounted for.

Temperature was 102° to 99° F. during the first week, after which it dropped to low grade or normal until death.

Roentgen examinations of the chest showed most intense azotemic edema on entry, April 18, 1950, with gradual improvement on subsequent examinations up to May 8, 1950, at which time the lung fields were almost clear. There was no history of blood transfusions, plasma or sulfa therapy prior to entrance into the hospital, however; it may be possible that the medicine which was given her by an outside doctor just prior to entrance may have been penicillin for her chest condition.

Muscle biopsy clinched the diagnosis of periarteritis nodosa and myositis.

Pathological Examination. Although no autopsy was obtained in this instance, the changes in the muscle biopsy presented clear-cut evidence of periarteritis. A number of vessels showed medial disruption due to eosinophil fibrinoid necrosis. Many inflammatory cells, polynuclear or mononuclear in character, were found in all coats of the vessels. Surrounding the vascular channels there was a predominant cluster of inflammatory cells. Scattered also throughout the muscle fibers was an eosinophilic, leukocytic, interfascicular, granulomatous reaction. Their alterations were highly characteristic of tissue hypersensitivity.

From an examination of this group of collagen diseases, it will be evident that they represent disturbances in which acute glomerulonephritis with antigenic (azotemic) edema plays a prominent part; that if the antigenic reaction is mild and collagenous destruction is slight, complete recovery may occur; but, that if it is severe, the patient may succumb at once. Or, the damage may not be great enough to cause immediate death, but may be sufficient to leave crippling effects on the collagenous tissue such that the patient may succumb at some later date. (Periarteritis nodosa is an example of this type.)

What, then, is the determining factor in the production of this striking lung picture? We have seen in such conditions as drug sensitization (Rich) that this type of so-called "azotemic edema" may result within a few hours after the administration of the drug. This type of reaction, when present, is accompanied by complete anuria. May it not be possible that the same sensitizing agent which gave rise to the anuria may also have caused the so-called "azotemic edema" found in the lung?

Trueta and his associates have demonstrated blanching of the parenchymal circulation of the kidney after injection of bacterial toxin into the renal circulation, thereby assuming almost the entire circulation to be shunted through the kidney without being subjected to parenchymal action, thus producing anuria. If Trueta should prove to be correct, is it not possible that a similar reaction might occur in the lung under the influence of the same toxic agent which caused the kidney reaction? Thus,

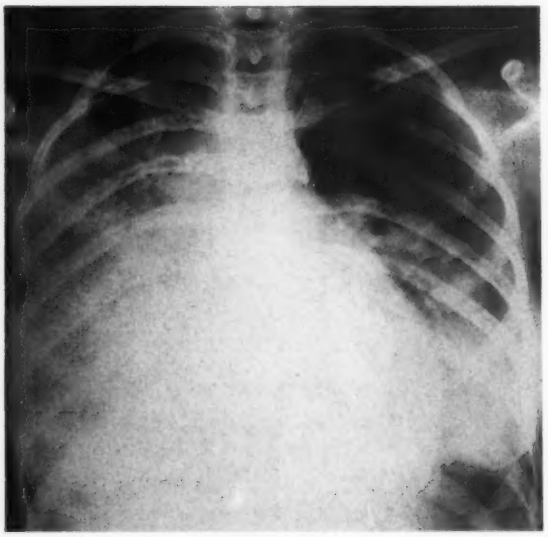

Fig. 8. Case viii. Rheumatic pneumonitis. Small blotchy areas of infiltration, coalescing to form massive areas of consolidation, present throughout almost entire right and lower half of left lung field. No pleural effusion. Some cardiac enlargement.

so-called "azotemic edema" of the lungs may not be a direct response to excessive urea and other nitrogenous waste products remaining in the blood because of suppression of urine, as the name implies, but may be due to a similar direct reaction of the lung to the influence of toxic material. Ischemia of the parenchymal circulation of the lung from the influence of toxin would explain the acute symptoms which accompany such a reaction, such as extreme cyanosis, dyspnea and shock. It would seem fitting, therefore, to replace the term "azotemic edema" with some more appropriate term such as "antigenic pulmonary edema."

In the second group of so-called "collagen diseases," rheumatic pneumonitis, disseminated lupus erythematosus, dermatomyositis, rheumatoid arthritis, and possibly scleroderma, the picture is different (Fox). In none of these diseases have we ever encountered antigenic pulmonary edema. All of these are more chronic in their course, often lasting over months or even years, with exacerbations of the disease and intervals of fairly normal health.

Much has been written about rheumatic pneumonitis, but no distinctive roentgenological picture has been indicated. In the early stages during the active development of the disease there may be vague areas of infiltration in the lung field, but these are not distinctive. Months later, areas of infiltration and even massive confluent areas of consolidation may appear which microscopically show evidence of rheumatic pneumonitis; at no time in our experience has there been any indication of acute antigenic (azotemic) edema. Indeed, the diagnosis is largely dependent upon the occurrence of multiple joint inflammation, often fleeting, during the course of the disease. It would seem that this may not have any actual relationship to acute polyarticular rheumatism such as we were used to thinking of in former days.

*Rheumatic Pneumonitis.**

Case viii (Fig. 8). R. B., white female, aged twelve, entered St. Mary's Hospital on August 3, 1949.

Past History. Ten weeks prior to entry she had a severe sore throat, lasting several days, which subsided under sulfa therapy.

Three weeks later she began to experience fleeting joint pains for the first time; most of the joints were involved. There was apparently no swelling or redness of the joints, but there were associated muscle pains. Dyspnea developed and gradually increased in severity.

About one month later (two weeks before admission), dyspnea became worse and she developed diaphoresis. A few days before entry she became anoretic and developed upper abdominal tenderness. Orthopnea followed with cough and blood-tinged sputum. No chest pain, epistaxis or vomiting.

Physical Examination. Well developed, white female in acute respiratory distress.

Lungs: Equal in size and in expansion. Tactile fremitus normal. Percussion note dull over both bases; crepitant rales both bases; increased harsh breath sounds over left lung field.

Heart: No thrills or rubs palpated; rhythm regular; apical and radial pulse 120 per minute. Apex beat left fifth interspace; heart tones poor quality. A rough to-and-fro continuous murmur

* Reported in detail, *J. Mo. State Med. Assn.*, 1950, *47*, 675.

was heard over the precordium, loudest at apex, transmitted to axilla. Inconsistent pericardial friction rub.

Abdomen: Soft; liver edge 3 cm. below costal margin; pulsated with each cardiac beat.

Extremities: Mild cyanosis of nailbeds. No petechiae. Trace of ankle edema.

Laboratory Findings. Blood: Erythrocyte count 3.25 million, hemoglobin 7.8 gm., leukocyte count 10,000, stab forms 2 per cent, segmental forms 67 per cent, lymphocytes 28 per cent and monocytes 3 per cent. Non-protein nitrogen 35 mg. per cent; Kahn test negative.

Urinalysis: Albumin and sugar trace; acetone present; few leukocytes and erythrocytes.

Roentgen Examination. Small blotchy areas of infiltration (coalescing to form massive areas of consolidation) are present throughout almost the entire right lung field and lower one-half of the left lung field. There is no definite roentgen evidence of pleural effusion. There is some cardiac enlargement.

The patient's course was steadily retrogressive, and she died within two days after admission.

Pathological Examination. Autopsy showed a typical microscopic picture of rheumatic pneumonitis. In the lung fields in this case there was again the widespread lung involvement with the distinctive changes of hyalin membrane lining alveolar walls, mononuclear and basophilic macrophages within the septa, and numerous "Masson bodies."

In 1937, Masson, Riopelle and Martin emphasized the presence of these "granulomatous intra-alveolar buds" in the lungs of patients dying from rheumatic fever. More recently, investigators have challenged the specific nature of these "Masson bodies," claiming that these structures can be found in lesions other than rheumatic pneumonia. Be that as it may, the quantitative formation is noteworthy in pure rheumatic fever and, again, these bodies are distinct from organized alveolar exudate with which they are commonly confused. Exclusive of the "Masson bodies," the other alterations represent the morphologic equivalents seen in instances of "malignant lupus," periarteritis nodosa and similar disorders.

Disseminated lupus erythematosus has a tendency to be more protracted in its course and more extensive in its effects than any of the other collagen diseases. It has a predilection for young women almost entirely. Its etiology is unknown and it almost always progresses to a fatal termination.

It involves primarily the vascular connective tissues, the endocardium and the serous membranes of the body cavities, and synovial membranes of joints.

Through its involvement of vascular structures, its effects are widely distributed throughout the organs and other structures of the body. Pericardial involvement may result in obliteration of the sac with thick plastic connective tissue. Endocardial involvement occurs in about one-third of the cases resulting in verrucous-like lesions on the heart valves, described by Libman and Sacks.

Similar effects may be produced in the pleural and abdominal cavities. Involvement of the vascular structures may result in perihepatitis and perisplenitis. The kidneys are large and swollen, and the glomeruli give the characteristic appearance of bent "wire loops."

Skin lesions are usually encountered at some time during the disease. They usually appear on the face forming a "butterfly pattern" across the nose onto the cheeks. The skin eruption may appear elsewhere on the neck, "V"-shaped exposed portion of the chest or even on the extremities. It may be transitory, but it is usually present at some time during the course of the disease (Klemperer, Pollack and Baehr). The skin eruption may fade long, often years, before the disease comes to its fatal ending.

During the course of the disease, the lung fields do not show any indication of antigenic edematous reaction such as that shown in the previously described diseases; there is little, if any, indication of lung involvement of any sort up to the terminal stage of the disease. Small irregular areas of infiltration, together with some increase in the lung markings, are all that is seen until just before the final stage when edema of

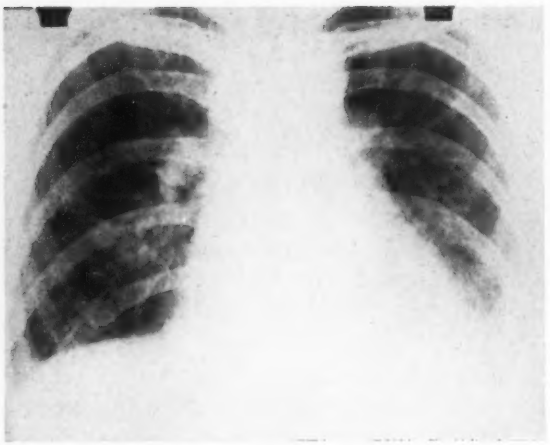

Fig. 9. Case ix. Disseminated lupus erythematosus, late in the disease showing blotchy areas of infiltration irregularly distributed throughout both lung fields; no edema; roentgen appearance not so severe as patient's condition indicated. Death seven days later.

the ordinary variety may occur. While edema of the subcutaneous tissues, to some extent, is a common finding in the terminal stage, there is nothing in the lung manifestations of this disease to simulate an acute sensitization reaction similar to that produced by the other diseases previously mentioned. This is in further support of the statement made by Baehr and Pollack, "In all our long experience with these diseases we have never encountered a lupus patient with eosinophilia, urticaria, asthma or any other clinical manifestation of allergy." A single case reported in the literature (Fox), and one of our own, might seem to challenge this statement; the possibility of coincident allergic affection from other cause, however, might easily explain such chance observations.

Disseminated lupus erythematosus characterized by:

Protracted illness over a year which began during pregnancy—spontaneous abortion.

Skin eruption over nose, cheeks, neck and other parts of the body.

Chronic nephritis with subacute attacks of edema of extremities and body cavities, especially toward termination of disease.

Severe acute polyarthritis with sore throat and fever toward the end of the disease.

Anemia requiring five blood transfusions during course of disease.

Hypertension reaching a blood pressure of 200/100.

Apparent sensitization to iodides and salicylates, but no eosinophils were present in blood count.

Spontaneous subcutaneous conjunctival and gastric hemorrhages.

Roentgen examination of chest showing little evidence of pathology until near end of the disease when slight effusion developed. There was no evidence of "azotemic edema" at any time.

Case ix (Fig. 9). A. K., white female, aged thirty-five.

First admission to St. Mary's Hospital, September, 1947, with swelling of face and ankles for three days; six months pregnant; maculopapular rash over both tibiae.

Laboratory Findings. Urine: From negative to albumin 4 plus, with specific gravity 1.020. Blood: Plasma proteins 5.21 gm. per cent, albumin 3.69 gm. per cent, globulin 1.52 gm. per cent, chlorides 609 mg. per cent, uric acid 4.5 mg. per cent.

Patient improved under salt-free diet and medication, and was discharged.

Second admission, October 1, 1947. Spontaneous delivery of seven month non-viable fetus.

Rash had spread to the other areas since previous entry, now involving nose, face and neck. Blood pressure had again become high, and albumin appeared in the urine. She had several severe headaches, muscular twitchings and saw "lines."

Under therapy, blood pressure subsided, skin lesions improved, and albumin disappeared from urine; patient was discharged.

Last admission, August 16, 1948. Severe arthritis developed in July, 1948, patient stated; she went to Hot Springs for treatment; given sodium iodide and salicylates which was followed by urticaria; benadryl administered which caused nausea and vomiting. Adrenalin injection, followed in two days by re-establishment of eruption again all over body at sites of previous involvement. Lesions developed in the mouth and throat became sore. Eyelids and face became edematous.

Physical examination revealed reddened throat, loud wheezing, and musical rales throughout both lung fields. Blood pressure 160/100; normal heart tones; no edema of legs.

August 20, 1948: Sore throat; conjunctival hemorrhages; pulse 88, temperature 103° F. Streptomycin and penicillin given.

August 22, 1948: Superficial, tender mass appeared in right lower quadrant thought to be subcutaneous hemorrhage. Abdominal ascites 2 plus. During next week patient did not improve. O_2 inhalations were given; digitalization; five blood transfusions in order to maintain erythrocytes above 3.5 million.

September 5, 1948: Emesis of 10 cc. black material; pulse rapid and irregular; lungs filling with moist rales.

September 8, 1948: Plasma given; lungs more moist; patient cyanotic.

September 9, 1948: Patient died.

Laboratory Findings.

Urinalysis: Albumin 1 to 2 plus, with leukocytes and erythrocytes.

Blood: Leukocytes 2,400, hemoglobin 9.7 gm., erythrocytes 3.15 million, hematocrit 31 per cent Differential count: stab forms 2 per cent, segmental forms 63 per cent, lymphocytes 32 per cent, eosinophils 0 per cent, monocytes 0 per cent. Platelets 200,000 per cu. mm. Non-protein nitrogen 60 mg. per cent, sugar 94 mg. per cent, plasma protein 5.73 gm. per cent, albumin 2.49 gm. per cent, globulin 3.24 gm. per cent, uric acid 9.1 mg. per cent, cholesterol 200 mg. per cent, calcium 10.5 mg. per cent, phosphorus 3.3 mg. per cent, chlorides 630 mg. per cent, alkaline phosphatase 2.8 units. Kahn test negative.

Roentgen Examination, August 24, 1948. Revealed some increase in the bronchovascular markings of the lower lobes, but no parenchymatous pathology. A small amount of fluid was present in both costophrenic sinuses. No evidence of edema. On September 3, 1948, portable roentgen examination showed a blotchy appearance of both lung fields, which might be due to edema, but this was not of the azotemic type, nor was it as severe as the patient's condition indicated. No further roentgen examinations were available during the last week of the patient's life.

Pathological Examination. All pathologic features justifying a diagnosis of disseminated lupus erythematosus or, as it has recently been named "malignant lupus erythematosus," were present in this case. Many of the more recently stressed histopathologic findings were noted. The renal involvement was principally glomerular, with the vitreous wire loops well exemplified; also the intravascular hematoxylinophilic bodies in the glomerular capillaries stressed by Klemperer were pronounced. These hematoxylinophilic bodies were also found in the lung capillaries. These structures probably represent the lupus erythematosus cell found in marrow and blood of cases of disseminated lupus erythematosus.

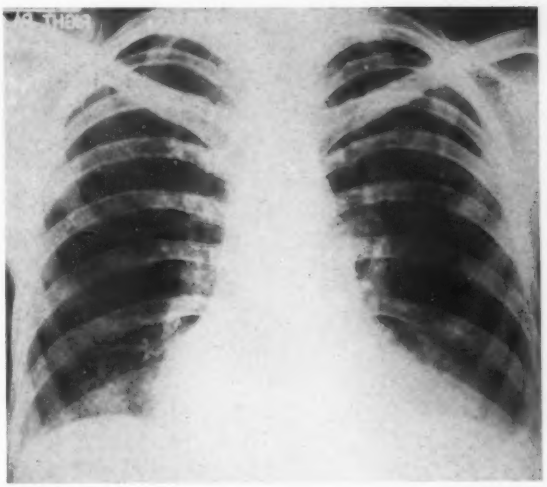

Fig. 10. Case x. Disseminated lupus erythematosus diagnosed by demonstration of "lupus erythematosus" cells in the bone marrow. Still living. No parenchymal involvement; no edema; possible slight effusion. Similar to findings in other cases at this early period of the disease.

The lung alterations were prominent. These consisted of focal areas of hyalin membrane linings, intra-alveolaredema, and interstitial mononuclear infiltrates. In some regions, fibroblasts had penetrated into the intra-alveolar exudate. The findings were morphologically similar to the lung lesions seen in the cases reported in this contribution.

Disseminated Lupus Erythematosus. Diagnosis by Demonstration of Lupus Erythematosus Cells in Bone Marrow.

Case x (Fig. 10). E. P., white female, aged thirty-three, admitted to St. Mary's Hospital on May 14, 1949.

Past History. Illness started three years before with swelling of ankles and wrists which later spread to hip joints. Fever of 103° to 104° F. accompanied by generalized aches and pains, swelling of eyes and headaches. Treated at another hospital by all manner of antibiotic agents without results. Gradually got better without further treatment. Developed a rash

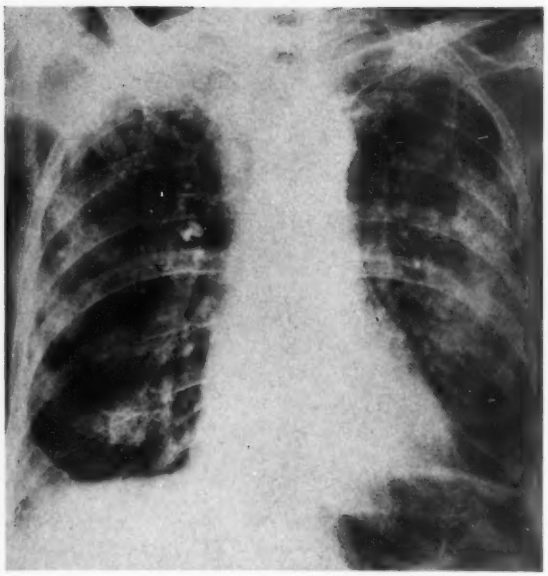

Fig. 11. Case xi. Scleroderma, generalized involvement. Parenchymal lung involvement does not occur until late in the disease. Near the end, small areas of infiltration appear irregularly scattered throughout the lung fields, especially mid-portion on the left. These do not appear very significant on roentgen examination but, on microscopic study, carry a distinctive picture.

over the bridge of the nose extending onto cheeks on either side in butterfly pattern, which persisted for five or six months and then faded and disappeared. She was better until one year ago when she developed "pneumonia." She says that she never really recovered from this in spite of treatment with antibiotics and other drugs.

Present Illness. Symptoms became worse; so she was admitted to the hospital for examination and treatment.

Physical Examination. White female, aged thirty-three, in extreme respiratory distress, orthopneic, sitting at edge of bed "to get her breath." By systems, examination was practically negative.

Chest: Negative.

Heart: Rapid rate, but normal.

Abdomen: Negative.

Extremities: Swollen and edematous.

Skin: "There is a papular rash over the neck and arms very closely resembling neurodermatitis. The skin over the lower extremities is thickened." There are many "lumps" in the skin of the neck which the patient states have been there for three years.

Laboratory Findings. Urinalysis: Negative. Leukocyte and erythrocyte blood counts, and hemoglobin consistently normal. Blood cultures negative. Guinea pig inoculation negative.

Sternal Puncture: Bone Marrow Examination. "The bone marrow was of the hyperplastic type, with granulocytes predominating. A number of cells were seen which appear to have nuclei somewhat similar to polymorphonuclear leukocytes, but with an enormous amount of phagocytized hyalin material. Cells such as these have been described as being found in the bone marrow in disseminated lupus by Malcolm M. Hargraves *et al.* These have been given the name of 'L. E.' cells."—G. O. Broun.

Roentgen Examination, May 14, 1949, at the time of great respiratory distress, did not show evident cause. There was an increase in lung markings extending out from the hilus regions into both lung fields, but there was no actual infiltration. There was slight pleural effusion in the costophrenic sinuses, but no other distinctive findings. The picture was similar to that found in other cases of the same disease. The cardiac shadow did not appear abnormal.

The patient is still alive; she continues to have exacerbations of dyspnea and edema.

Scleroderma, Generalized Involvement; Late Pulmonary Manifestation.

Case xi (Fig. 11). R. K., white male, aged fifty-nine, entered Firmin Desloge Hospital for the first time on December 1, 1947. On this and several other admissions over the next two years he complained of tense contraction and thickening of the skin all over his body, sensation of coldness, tingling of fingers, lethargy and lack of appetite.

Physical Examination. Thin, rather anemic, white male, with tense, board-like skin over the entire body. The fingers were intensely hard. No other evidence of organic pathology.

Pathological Examination. Biopsy: Microscopic examination of skin and subcutaneous tissues "shows irregularity of the collagenous tissue of the skin and subcutaneous tissues. The dermal papillae are made up of a dense fibrous tissue that is practically acellular. The rete pegs appear distorted by the fibrous tissue hypoplasia. The picture is compatible with a diagnosis of scleroderma."—R. Simon.

On first admission, December 1, 1947, urinalysis was negative.

Blood: Leukocytes 6,600 to 10,050, erythrocytes 4.92 million, albumin 2.62 to 4.23 gm. per

cent, globulin 2.59 to 1.78 gm. per cent, making total proteins 5.22 to 6.01 gm. per cent.

Blood pressure 104/70, temperature 98.8° F., respirations 20, pulse 64, average.

Roentgen Examination. Chest failed to reveal any evidence of pathology at this time. The esophagus, stomach and intestines, likewise, showed very little evidence of pathology at this time.

Further roentgen examination on February 5, 1948, showed that the gastrointestinal tract had assumed the characteristic appearance of scleroderma. There was:

Esophageal shortening, irregularity and narrowing in the lower one-third with peptic ulcer (dilatation of middle one-third).

Stomach showed increased prominence of rugae and pronounced hypomotility; one-half of the barium meal remaining for nine hours.

Duodenum and *small intestine:* Increase in size of the lumen of the duodenum with coarsening of the mucosal folds; extreme hypomotility of small intestine, requiring nine hours to reach the cecum. Small intestine showed irregular areas of constriction and dilatation, typically found in scleroderma.

These findings became more and more pronounced up to the time of the patient's death.

On final admission, October 26, 1949, all of his symptoms had become intensified; he had lost 90 pounds in weight and had developed a cough with expectoration and fever. Dyspnea became so severe that he required oxygen inhalation; vomiting and diarrhea developed.

Re-examination on November 9, 1949, revealed small areas of infiltration throughout the lungs, especially in the mid portion of the left lung field; these were not present at previous examination. The remaining portions of the lung were unchanged.

On November 17, 1949, he became comatose; the next day the patient died.

Pathological Examination. The morbid anatomy of this case revealed a full blown, well advanced example of scleroderma. Briefly stated, there was well marked collagenization of the dermis, with rete peg atrophy; the glomeruli showed a stiffening of the basement membrane; osteoporosis was pronounced, and the esophagus showed a deep sclerotic ulcer with the characteristic collagen change of scleroderma.

The lungs, which are of paramount importance in a consideration of the cases under discussion, revealed a dense sclerocystic transformation. The process in the lungs was generalized, well advanced, and old in point of time. In this case it is difficult to find any earlier lesions which would be reminiscent of tissue hypersensitivity. Judged by this example, it is difficult to see a connecting link warranting the categorization of scleroderma with other forms of tissue hypersensitivity. Examples of scleroderma have never been too readily accepted as being a component part of the patho-anatomic complex of collagen diseases.

Analysis of the roentgen findings in this second group of diseases, comprising rheumatic pneumonitis lupus erythematosus, dermatomyositis and sclerodermatitis, would indicate that an entirely different type of reaction occurs. The process is more chronic, often lasting over months or years, with intermittent bouts of nephritis and subcutaneous edema, but without any evidence of lung involvement until the terminal stages. At this time pulmonary edema may occur, but it is never of the acute azotemic type. There may be small, irregular collagenous deposits throughout the lung fields, or these may coalesce into massive areas of consolidation as in rheumatic pneumonitis.

Comment on Pathological Findings. Within recent years, following the original data laid down by Klinge and Vaubel, a morphological similarity has been noted between the heterogeneous group of disorders, such as idiopathic periarteritis nodosa, disseminated lupus erythematosus, rheumatic fever, and tissue hypersensitivity due to various antigens. But a word of warning should be issued in that morphological similarity does not, of necessity, mean unity of causation. Although, bearing in mind Rich's investigation, the pivotal pathology in the lung suggests: first, recent or remote antigen-antibody conflict; second, exclusive of the vascular changes, the exudative and proliferative alterations in the lung are worthy of emphasis.

SUMMARY AND CONCLUSIONS

1. Pathological examination of the lungs reveals a striking similarity in most of the collagen diseases.

2. Roentgenologically, the collagen dis-

eases seem to be divided into two major groups:

A. Those in which there is an acute antigenic response, associated with glomerulonephritis and antigenic (azotemic) pulmonary edema.

B. Those in which there is no indication of lung reaction up to the terminal stages of the disease. At this time, pulmonary edema may occur, but it is never of the azotemic type, but rather, irregular collagenous deposits throughout the lung field.

Roentgen examination should be of aid in differentiating these two groups.

3. The mere fact of common connective tissue involvement in all of these diseases does not preclude the possibility of a number of etiological agents with consequent variation in response of the tissues. It may be found that such agents may also include bacterial and virus toxins of various strains and types which may, depending upon the conditions present in the body, produce a wide variety of manifestations in the tissues.

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DISCUSSION

Dr. Fred Jenner Hodges, Ann Arbor, Michigan. Drs. Sante and Wyatt have been helpful in bringing into focus the currently emphasized collagen diseases; all of the nine disease entities which have been problem cases for internists. As such, patients are subjected to all manner of diagnostic procedures in the hope of learning the true state of affairs.

It is well for radiologists to attempt to find some solid ground in the form of objective roentgen evidence to assist in the perplexing matter of differential diagnosis.

I read the authors' paper with considerable interest, at first with a good deal of perplexity, but later with an appreciation of its real interest for diagnostic radiologists. Our own experience with patients of this sort is certainly not great, and I find, in trying to review it, that it is

a pretty muddled conglomeration of obscure diagnostic difficulties.

What the authors had to say about lupus erythematosus is of particular interest to me because we have been plagued with one particular patient who has been sick over a considerable period of time, during which a great variety of diagnoses have been entertained and ultimately discarded. The final diagnosis was reached, as is commonly true when short of the autopsy table, by exclusion.

In our files, there are a large number of roentgenograms of this patient covering a considerable period of time, the majority of them showing no abnormality. On the other hand, there are fully eight or ten episodes in her history, which covers some three or four years, on which occasions the chest findings have been truly alarming. These abnormalities disappear very quickly.

Before coming to this meeting, I reviewed those films searching for some pattern that would be helpful in identifying the condition. I must admit that no such pattern was discovered. We found evidences of pulmonary edema, azotemic or not I do not know, but appearing very much like early lobar pneumonia, associated very frequently in the course of this patient's career with some pleural fluid (not much, but frequently in the fissure between the lower and middle lobes). On two or three occasions there was mild but recognizable evidence of pericardial effusion. The abnormal pulmonary findings were invariably of fleeting duration.

I am a little disappointed to find that the disease is felt to be one that does not lend itself well to roentgen recognition. I am inclined to believe that this is correct. It is surprising to find that in the experiences here reported positive roentgen findings are to be expected only in the very late stages of the disease. Our patient, a young woman, is in the best health she has enjoyed for a good many months, and as yet has not been admitted to the ACTH ranks of those who are in the closing stages of their disease.

Today many patients with obscure disease conditions are subjected to early and energetic treatment with antibiotic agents which are fully capable of so altering well known roentgenologic chest findings as to be very, very confusing.

It is well to bear that thought in mind, because of all patients one is apt to see, those in whom the nine situations which the authors have listed appear are very apt to be subjected to all sorts of therapeutic attempts without sound rationale. Under such circumstances the radiologist may have great difficulty in assaying his findings.

While we cannot take home from this presentation iron-clad roentgen diagnostic signs for each of the collagen diseases, Drs. Sante and Wyatt have given us much food for thought.

THE ROENTGENOLOGIC MANIFESTATIONS OF AMEBIASIS OF THE LIVER WITH CONCOMITANT FINDINGS IN THE CHEST*

By SAMUEL SCHORR, M.D., *and* ARMIN SCHWARTZ, M.D.
JERUSALEM, ISRAEL

IN COUNTRIES where amebiasis is endemic, the possibility of amebiasis of the liver with thoracic involvement should always be borne in mind. Thoracic involvement in amebiasis is often confused with other pulmonary conditions because of the similarity of symptoms and signs. Early recognition of amebiasis of the chest is of great importance since immediate anti-amebic treatment may effect cure, or at least prevent further progress towards abscess formation. Difference of opinion exists concerning the pathogenesis of amebic pleuropulmonary complications. This, however, will not be dealt with in this paper.

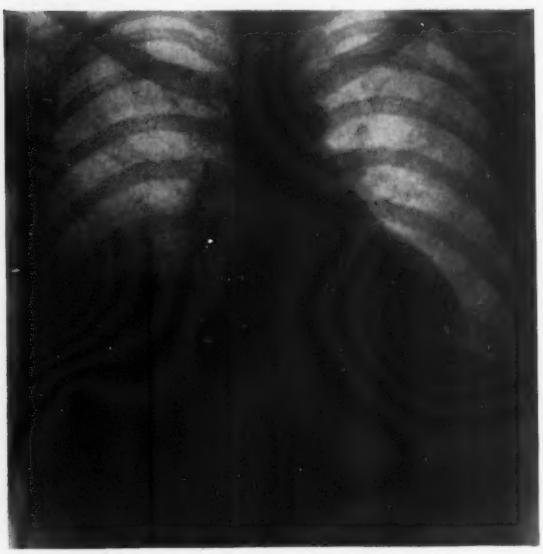

FIG. 1. The right diaphragm is elevated; its outline blurred. There is a slight density in the lower right lung field. The right costophrenic angle is clouded with some fluid in the periphery of the right chest.

This twenty-seven year old female had elevated temperature during the three weeks before admission with severe pain in the right upper abdomen. The liver was markedly tender. Leukocyte count, 12,200; erythrocyte sedimentation rate, 4 mm. per hour (Linsenmayer); temperature, 38° C. Anti-amebic treatment resulted in marked improvement.

Little attention has been paid to the roentgenologic chest manifestations of amebiasis. These may give the clinician the first clue to the diagnosis or may support the clinical impression. The roentgenologic manifestations described merely indicate that a subdiaphragmatic condition exists. The roentgen findings considered separately are in no way pathognomonic for amebiasis, but if present together, they point to this possibility.

The roentgen appearance varies considerably according to the stage of the disease, the location of the amebic process, and the extent and degree of hepatic and thoracic involvement. As a rule, the roentgenologic findings become more positive in the more advanced stages of amebiasis. The various stages of the amebic process may therefore be followed roentgenologically.

This study is based on 49 cases of amebiasis of the liver and the chest treated in this hospital during the last seven years. A total of 170 cases was examined but only those in which typical, unequivocal, clinical, laboratory, roentgenographic and roentgenoscopic findings were found, were included in this paper.

Sixteen cases showed roentgen evidence of chest involvement. Seven had fluid at the base of the right chest. In 2 cases, the left chest was involved in addition to the right. In 1 case the left chest only was involved. Six had patchy infiltration of the right

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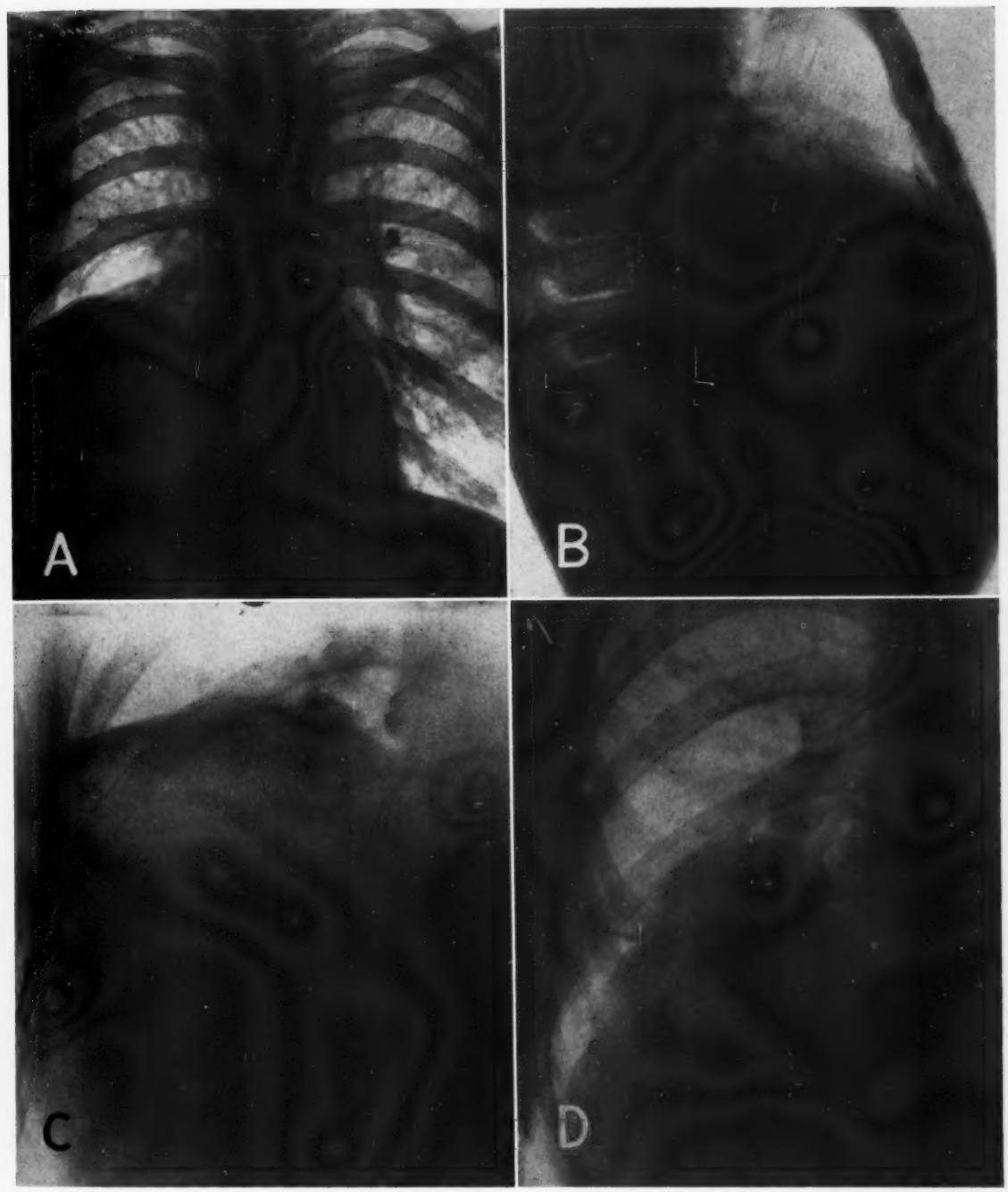

Fig. 2. (*A*) October 31, 1947. The right diaphragm is elevated, deformed and fixed. (*B*) October 31, 1947. Right lateral roentgenogram. Note the clouded anterior costophrenic angle. (*C*) November 2, 1947. Fluid at the base of the right chest. (*D*) December 8, 1947. Note the bulging into the right lower lung field after aspiration of 200 cc. of sterile pus by pleural puncture.

Fig. 3. Gallbladder filled with contrast medium displaced downward and laterally by space-occupying process in the central portion of the liver.

lower lung field with some fluid in the right chest and 2 had lung abscesses. In 33 cases, involvement of only the right diaphragm was present. Nine patients complained of pain in the lower region of the right chest.

During the early stages of amebic hepatitis (this term according to Sodeman and Lewis[2] is used to indicate the early phase of the condition before abscess can be diagnosed), the roentgen findings are limited to a general enlargement of the liver shadow, elevation of the right diaphragm with restriction of its mobility (occasionally with paradoxic movement) or its complete immobilization (Fig. 4*A*). The contours of the right diaphragm become hazy and indistinct; the diaphragm flattens; the costophrenic sinus becomes clouded (Fig. 1).

When a solitary amebic abscess is formed, the roentgen findings become more localized and definite. They may be found, however, only when the abscess is situated at the hepatic periphery, especially near the diaphragm. A distinct, localized, upward bulging of the diaphragm into the right lower lung field may then be seen in both the posteroanterior and lateral roentgenograms (Fig. 2, *A*, *B*, *C*, and *D*). This bulging is accompanied by an elevation of the right diaphragm and impairment of its mobility.

An abscess in the right lateral zone of the liver causes bulging of the lower portion of the chest and widening of the intercostal spaces. An abscess in the central or lower portion of the liver may be recognized only if it is very large, partly calcified, or if the contrast medium filled gallbladder is displaced downward and laterally (Fig. 3). If air is introduced into the abscess cavity, a fluid level will be seen in the liver shadow in the erect position and a round radiolucent area will be seen in the prone position (Fig. 4, *A*, *B*, *C*, and *D*).

Multiple adhesions may develop between the upper surface of the liver and the base of the right chest, indicating that the process gradually invaded the diaphragm. In 2 patients in whom a bulge was observed in the upper middle portion of the right diaphragm, pneumoperitoneum was performed in order to visualize the liver contours. Air surrounded the upper margin of the liver except for an area 6 to 7 cm. in length corresponding to the bulge; air was not seen in this region in all roentgenograms taken in various positions (Fig. 5, *A*, *B*).

Alterations in the cardiophrenic and costophrenic angles are significant. Progressive elevation of the diaphragm or the sudden clouding and obliteration of the acute cardiophrenic or costophrenic angle may indicate pending perforation of the liver abscess. Walters *et al.*[3] report 2 cases of sudden perforation of an unsuspected asymptomatic amebic liver abscess, roentgenograms of which showed progressive elevation of the right diaphragm and clouding of the cardiophrenic and costophrenic angles.

Reduced mobility of the right diaphragm may also be caused by acute liver or gall-

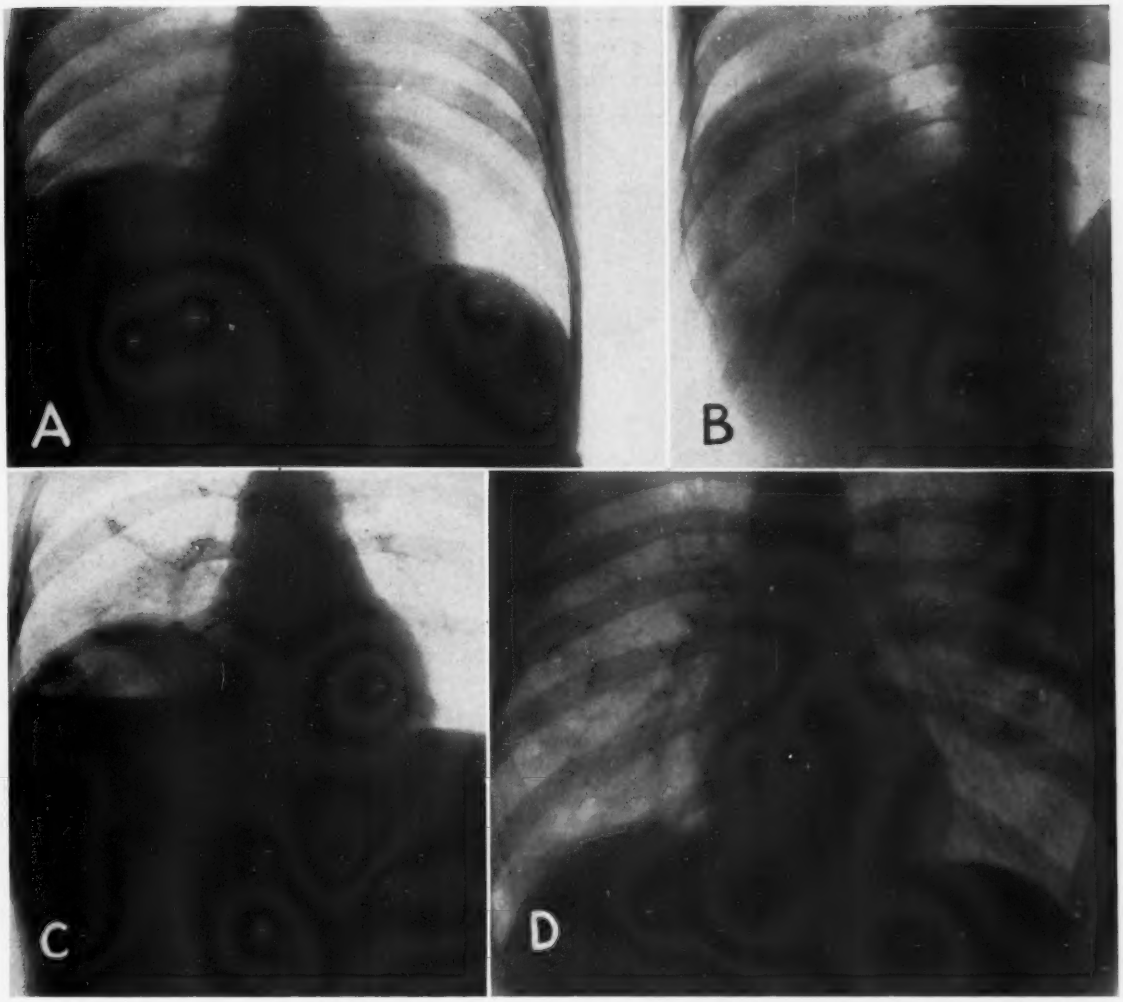

Fig. 4. (*A*) July 25, 1948. The right diaphragm is elevated with indistinct outline; the right costophrenic angle is clouded. (*B*) August 4, 1948. Roentgenogram (Bucky grid) in recumbent position (after evacuation of 700 cc. of pus). Elevated right diaphragm. The costophrenic and cardiophrenic angles are free. An oval radiolucent area is clearly visible in the right liver shadow. (*C*) August 4, 1948. Roentgenogram in erect position. Fluid level with a radiolucent area above it. On roentgenoscopy, restricted movement of the right diaphragm observed. No chest involvement. (*D*) September 28, 1949. Normal position of the right diaphragm with normal movements.

This male, aged forty-two, had increasing pain in the right upper abdomen and elevation of temperature for the nine months preceding admission. There was no cough. Two weeks before admission, the temperature went up to 39° C. On admission, the liver was markedly enlarged and tender. Leukocyte count, 16,000; erythrocyte sedimentation rate, 17 mm. per hour; stool, negative for ameba. There was no improvement on emetine treatment. Liver puncture produced 350 cc. of sterile pus; two days later, a second liver puncture gave the same amount of pus. No amebas could be found in the pus. There was remarkable improvement after the second liver puncture.

bladder inflammations such as cholecystitis, empyema of the gallbladder, etc., but in such conditions, there is no marked elevation of the diaphragm unless a concurrent subphrenic process is present. The diaphragm may be markedly elevated, on the other hand, in such conditions of the liver as tumors, metastases, echinococcus cysts, etc., but in those cases, there is no restriction of diaphragmatic mobility. Of our 49 cases of proved amebiasis of the liver, cholecystography was performed in 13 cases; in only 1 case was the gallbladder not filled. The differential diagnosis of amebiasis with a nonspecific subphrenic inflammatory process such as paranephric abscess is sometimes very difficult. In the latter condition, the posterior costophrenic angle as seen in the lateral roentgenogram is obliterated, whereas in amebiasis the anterior one is involved (Fig. 2*B*).

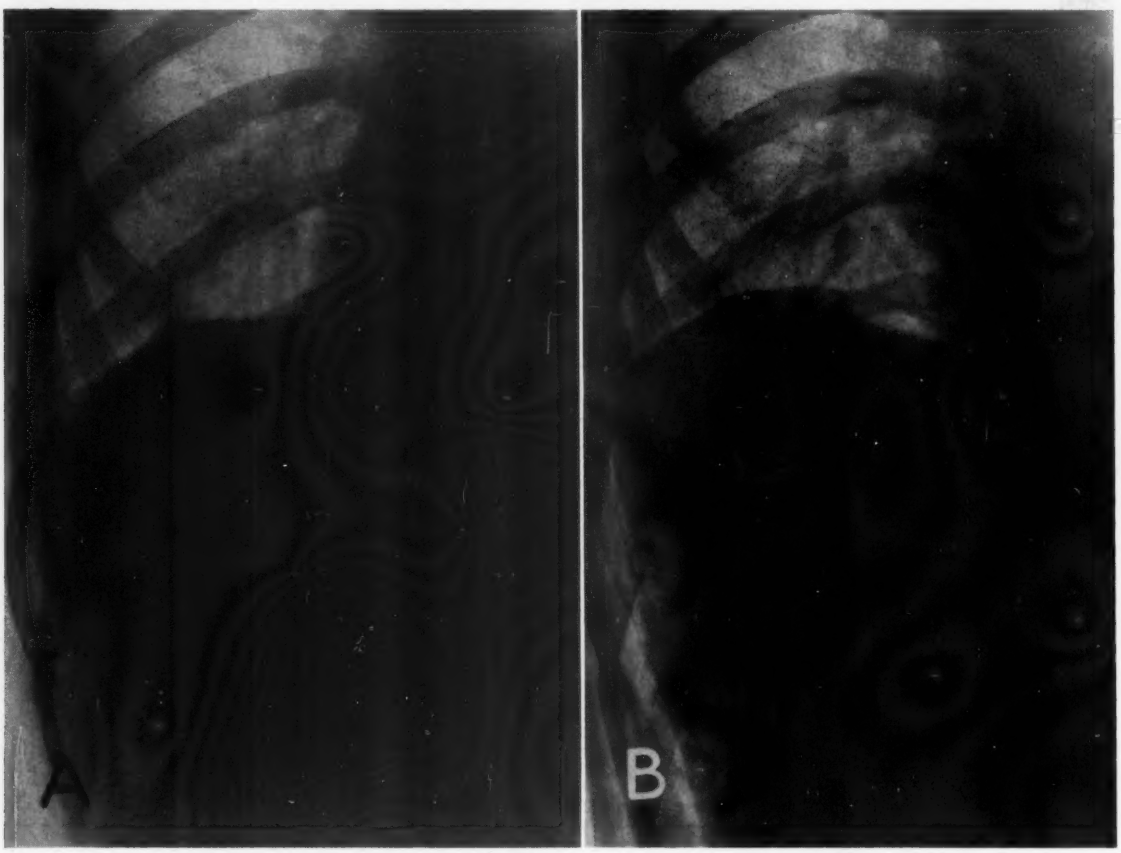

Fig. 5. (*A*) Deformed right diaphragm with a density extending from its central portion upward. (*B*) Pneumoperitoneum (after improvement due to emetine). Air around the liver except the lateral half of its diaphragmatic surface.

This male, aged twenty-six, had dysentery with bloody stools three years ago. During the last two years, he was admitted several times to hospitals in Teheran for chest complaints. On admission to our hospital, he complained of high fever, cough and stabbing pain in the right chest. The pain became worse with deep breathing.

In the right lower lung field, infiltrative patches which tend to coalesce may appear, producing homogeneous clouding with indistinct borders. These patches may be due to foci of atelectasis, pneumonia, or to

actual amebic pneumonitis. The latter occurs in those cases in which the amebic process has progressed through the diaphragm into the base of the right lung. In these cases, transverse band-shaped shadows, such as occur in other non-amebic subphrenic processes, may be seen at the base of the right lung, and may be interpreted (Fleischner[1]) as plate-shaped foci of atelectasis (Fig. 6, *A*, *B* and *C*).

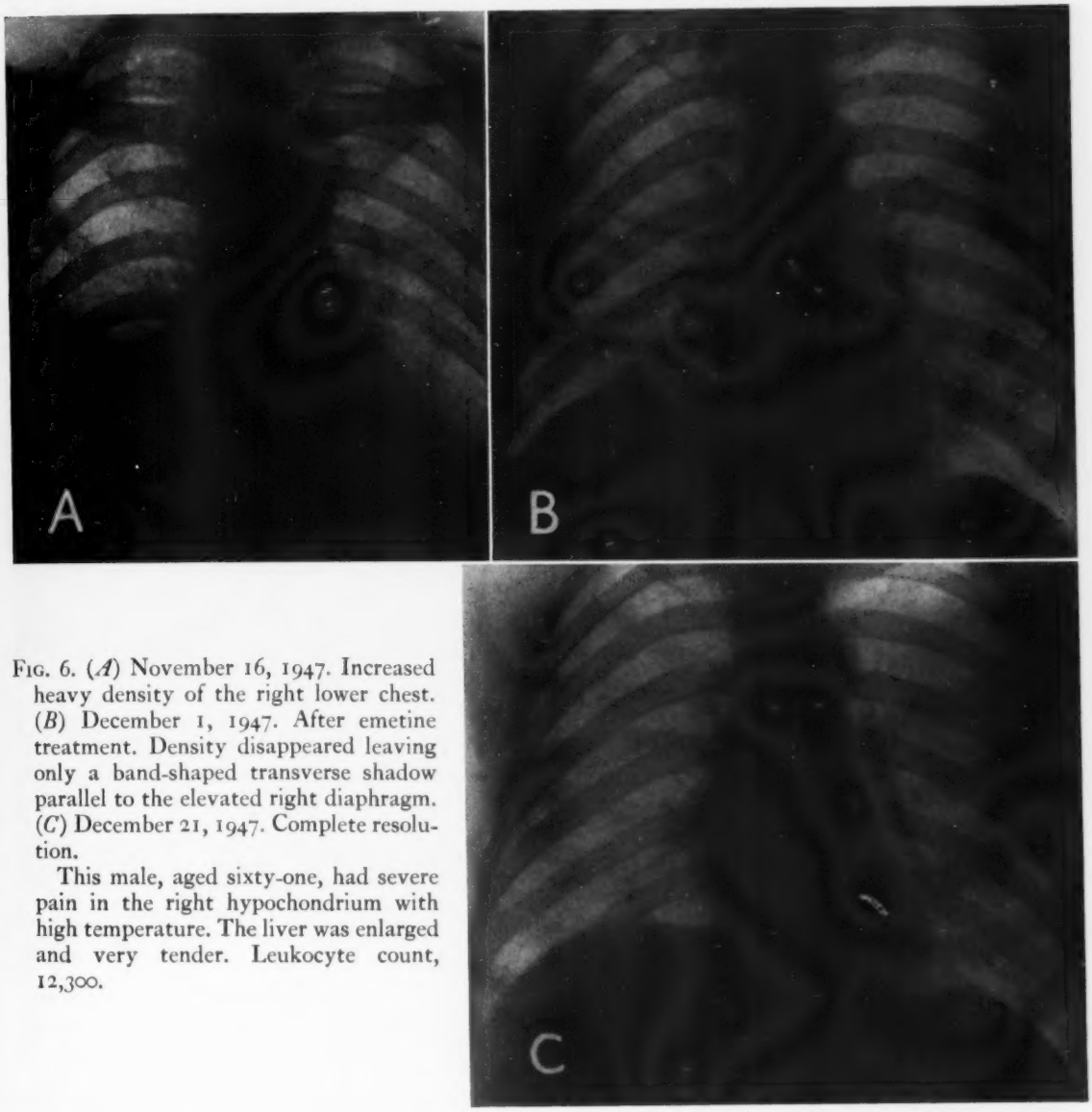

Fig. 6. (*A*) November 16, 1947. Increased heavy density of the right lower chest. (*B*) December 1, 1947. After emetine treatment. Density disappeared leaving only a band-shaped transverse shadow parallel to the elevated right diaphragm. (*C*) December 21, 1947. Complete resolution.

This male, aged sixty-one, had severe pain in the right hypochondrium with high temperature. The liver was enlarged and very tender. Leukocyte count, 12,300.

An irregular clouded area including a cavity with a fluid level may develop in the lung, indicating the possibility of an amebic pulmonary abscess (Fig. 7, *A*, *B*, *C*; 8 *A*, *B*). The pneumonic process may be accompanied by varying degrees of pleural reaction and involvement of the diaphragm. In rare instances, the left chest is involved; most probably a reaction or spread from the left lobe of the liver (Fig. 9).

In several cases, the roentgenograms (Fig. 7, 10, 11, *A*, *B*) show a string-like shadow proceeding perpendicularly from the localized bulge of the diaphragm to the

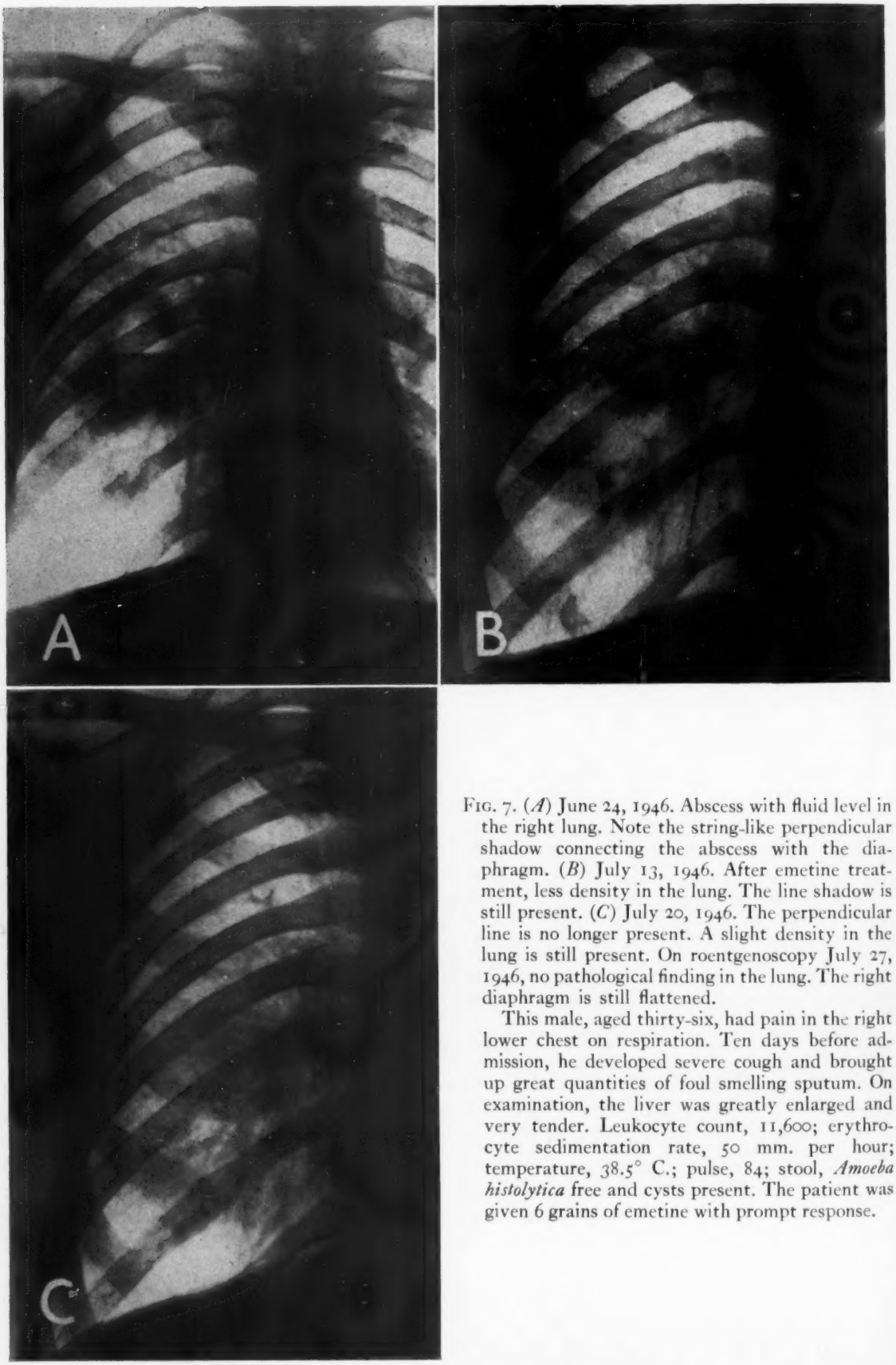

Fig. 7. (*A*) June 24, 1946. Abscess with fluid level in the right lung. Note the string-like perpendicular shadow connecting the abscess with the diaphragm. (*B*) July 13, 1946. After emetine treatment, less density in the lung. The line shadow is still present. (*C*) July 20, 1946. The perpendicular line is no longer present. A slight density in the lung is still present. On roentgenoscopy July 27, 1946, no pathological finding in the lung. The right diaphragm is still flattened.

This male, aged thirty-six, had pain in the right lower chest on respiration. Ten days before admission, he developed severe cough and brought up great quantities of foul smelling sputum. On examination, the liver was greatly enlarged and very tender. Leukocyte count, 11,600; erythrocyte sedimentation rate, 50 mm. per hour; temperature, 38.5° C.; pulse, 84; stool, *Amoeba histolytica* free and cysts present. The patient was given 6 grains of emetine with prompt response.

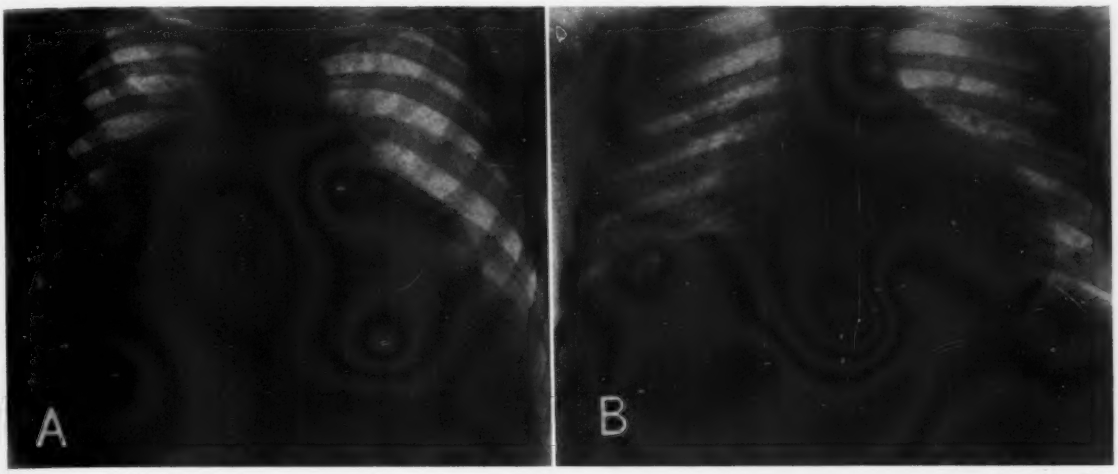

Fig. 8. (*A*) Density in the right lower lung field with a radiolucent area with a fluid level—pulmonary abscess. (*B*) Three weeks after anti-amebic treatment a small residual density in the right lung only.

This six year old boy was admitted with temperature and cough of one week's duration. On admission, his temperature was 38.5° C., the liver was greatly enlarged and very tender. Leukocyte count, 21,000; erythrocyte sedimentation rate, 10 mm. per hour; stool, no amebas. Emetine treatment resulted in marked improvement in his general condition; leukocyte count and erythrocyte sedimentation rate returned to normal.

pneumonic shadows in the lung. In view of the fact that these perpendicular linear shadows were observed in cases of proved amebiasis and disappeared after anti-amebic treatment, it may be assumed that they are indicative of the spread of the inflammatory process. Such shadows when combined with other roentgenologic signs described above should induce the roentgenologist to consider the possibility of amebiasis.

Fig. 9. Roentgenogram shows fluid in the left chest. On roentgenoscopy, after two weeks of emetine treatment, no fluid.

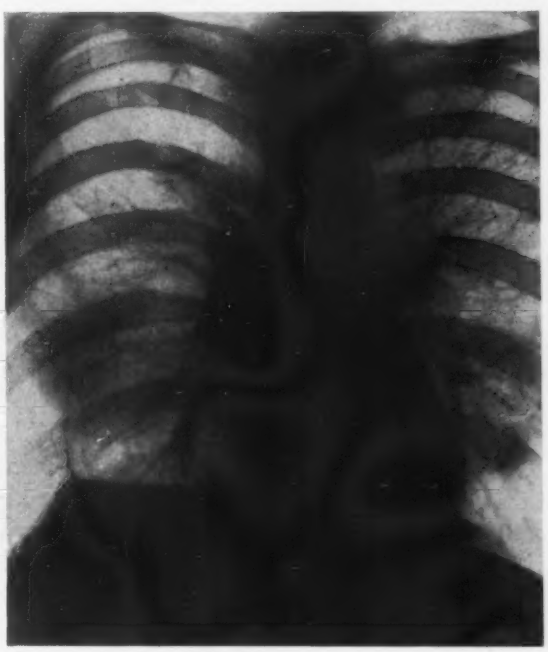

Fig. 10. This roentgenogram shows a deformed, immobile right diaphragm and a perpendicular shadow leading to a density in the right lower lung.

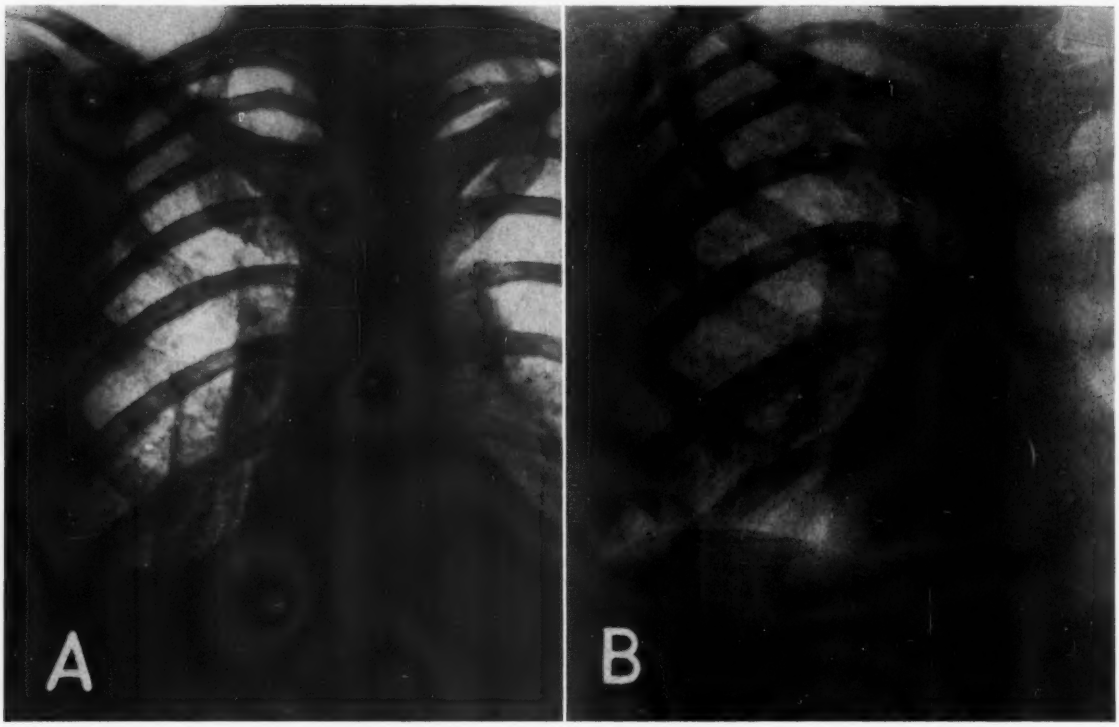

Fig. 11. (*A*) July 25, 1949. Note the perpendicular shadow from the diaphragm upwards. (Emetine treatment was started on July 23, 1949.) (*B*) September 14, 1949. The perpendicular shadow is no longer visible.

This female, aged thirty-two, had, five weeks before admission, temperature up to 39° C. with heavy cough; brought up great quantities of foul smelling sputum. On admission July 22, 1946, leukocyte count, 12,400; temperature, 37.8° C. After anti-amebic treatment, temperature returned to normal; cough and pain disappeared.

SUMMARY

The roentgenological manifestations of hepatic and chest amebiasis as observed in a series of forty-nine cases of proved amebiasis are described.

The first changes are limited to an enlargement of the liver shadow, elevation of the right leaf of the diaphragm and restriction of its mobility. These changes might correspond to amebic hepatitis without chest involvement.

A localized bulging of the right diaphragm into the lower right lung field denotes a solitary amebic liver abscess.

Chest involvement comprises obliteration of the costophrenic or cardiophrenic sinuses, pleural effusion, and pneumonic consolidation with or without abscess formation.

A linear string-like perpendicular shadow may be seen in the right lower lung field in addition to a fixed and deformed diaphragm. This last roentgen finding might be an additional aid in the diagnosis of amebiasis of the chest and worthy of further study.

When dealing with pathology in the right side of the chest (pleurisy, empyema, basal pneumonia, abscess of lung), the possibility of amebiasis of the chest should always be borne in mind, particularly in countries where amebiasis is endemic.

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INTRA-ARTERIAL CATHETERIZATION OF VISCERA IN MAN*

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THE afferent artery from which a neoplasm obtains its blood supply represents a route of attack on such growth, with diagnostic and possibly therapeutic implications. In 1938, Wood[21] showed that the chief blood supply of primary cancer of the lungs in man is from the bronchial arteries, rather than the main pulmonary vessels which serve the major portion of the organ. More recently, Breedis and Young[1] observed that the main blood supply to neoplasms in the liver of mice, whether transplanted, spontaneous, or metastatic, and to metastatic neoplasms of the liver in man is derived from branches of the hepatic artery, in contrast to the normal parenchyma of the liver, whose main blood supply is from the branches of the portal vein.[6] Thus, if the bronchial arteries of the lung, or the hepatic artery of the liver could be entered, distortions by tumors of vascular patterns as visualized by radiopaque substances introduced into the arteries might provide diagnostic information of value.

The visualization of the arterial supply to specific organs has been accomplished roentgenographically by using radiopaque media, and the alteration of the normal pattern of vessels has been of value in detecting or outlining tumors, particularly in the brain and thorax.[12,16,19] Demonstration of vascular patterns within the abdomen by intravenous administration of radiopaque material, however, has not been satisfactory. Several investigators[5,11,15,20] have demonstrated the vascular pattern of some abdominal viscera by radiopaque substances introduced into the aorta through direct aortic puncture. Although only a few untoward reactions were reported, the fear and dangers of a blind puncture of the aorta with possible extravasation of the injected material and aortic blood into the tissues have discouraged the wide use of this technique.

Fariñas[8] performed aortography by retrograde injection of radiopaque materials via the femoral artery. He had previously achieved similar results by passing a catheter from the femoral artery up the aorta.[7] The employment of the intracardiac catheter by Cournand and his associates[4] has proved to be a relatively simple procedure. Radner[17] first passed a ureteral catheter from the radial artery into the arch of the aorta, and Brodén *et al.*,[2] using this technique, catheterized the ascending aorta in 3 patients with congenital aortic anomalies. Jönsson visualized the aortic valves, sinus of Valsalva and the coronary arteries by injecting contrast media into the ascending aorta via an arterial catheter. No untoward cardiac or electrocardiographic changes were noted.[13]

Radner[18] was able to obtain a subclavian angiogram by injection of contrast medium by retrograde catheter into the subclavian artery proximal to an obstructing cuff. By this method he demonstrated a metastatic tumor by its increased vascularity. Brodén *et al.*[3] reviewed their method stressing the

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problems of vascular spasm, difficulty in directing the catheter to the aorta and into the correct position in the aortic arch for demonstrating patent ductus Botalli. Catheterization of the left heart in man has been reported[10,22] but has proved hazardous. The deaths and untoward effects in man and animals were encountered with the introduction of the catheter into the left ventricle, and no reaction was noted in passing the catheter through the arteries.[9]

If the major artery leading to a specific organ could be isolated to the exclusion of other viscera, not only could that specific organ be visualized roentgenographically, but also various chemotherapeutic agents could be administered in high concentration directly to neoplastic lesions involving this organ. Furthermore, such an isolation of the arterial supply of such an organ in vivo would enable the employment of this method for many pharmacological and physiological studies. In the search for clinical methods by means of which the afferent artery to deep-seated neoplasms could be reached, the feasibility of intra-arterial catheterization of viscera was explored. This communication reports the development of the method.

MATERIALS AND METHODS

The investigations were carried out by a team of a surgeon, radiologist, internist and anesthetist. Radiopaque, intracardiac catheters, 100 to 150 cm. long, No. 6 to No. 9F with a fixed curve at the tip, were used.

The technique was first tried on cadavers. By passing the catheter from the carotid or brachial arteries into the aorta, it was found that introduction of the catheter into various branches of the aorta could be accomplished. With practice, satisfactory adeptness was achieved in entering the celiac axis, superior mesenteric, inferior mesenteric, renal and iliac arteries. Likewise, it was found both carotids and subclavian arteries and their smaller branches could be entered by catheters introduced into either femoral artery. It was determined, however, that retrograde arterial catheterization through the femoral artery did not afford a satisfactory technique for inserting the catheter into small branches of the aorta because of the obtuse angle and the distal lip such vessels have at the point of branching (Fig. 1*A*). Occasionally the renal arteries can be catheterized via the femoral artery. For these reasons, the insertion of the catheter through the carotid and brachial arteries appeared more feasible.

Twenty-eight arterial catheterizations were then performed on 24 patients with metastases from various neoplastic diseases. The procedure in its entirety, including the hazards, risk and experimental nature, was explained fully to each patient and an unqualified agreement was obtained in all cases.

Catheterization Technique. The procedure in adults is carried out under routine preoperative medication and local procaine anesthesia. The 3 children in this series had a general anesthetic; the 2 eldest had nitrous oxide and the fourteen month old received ether. The artery is exposed in the supraclavicular area and loops of *thin*, flexible rubber tubing or rubber bands are placed around the vessel above and below the site for the opening of the artery (Fig. 1). Hard rubber tubing should not be used because it may obstruct the blood flow. A 2 mm. longitudinal incision is made through the wall of the artery with a small scalpel and the tip of the catheter is inserted. The right common carotid or either brachial artery is preferred to the left carotid artery for aortic catheterization. The catheter was passed down the left common carotid artery in 1 patient (G.B.), and although the descending aorta was finally entered, the acute angle formed by the left carotid artery and the arch of the aorta made it difficult to pass the catheter distally. Furthermore, the control of the position of the tip is not as easy from the right carotid artery. Tension of the rubber loops about the artery tightens the edges of the incision about the catheter and effectively prevents bleeding. The catheter is filled with saline containing 2 mg. per 100 cc. of heparin before insertion, and this solution is kept running slowly through the catheter during the procedure at a rate of 20 to 30 drops a minute from a reservoir hung at a height sufficient to exceed the systolic pressure (usually 6 feet above heart level). A three-way stopcock at the end simplifies administration of radiopaque medium and other materials.

After insertion into the artery, the catheter is guided by roentgenoscopy. A sterile sheet is draped over the surgical field to avoid contamination by the roentgenoscopic screen in the

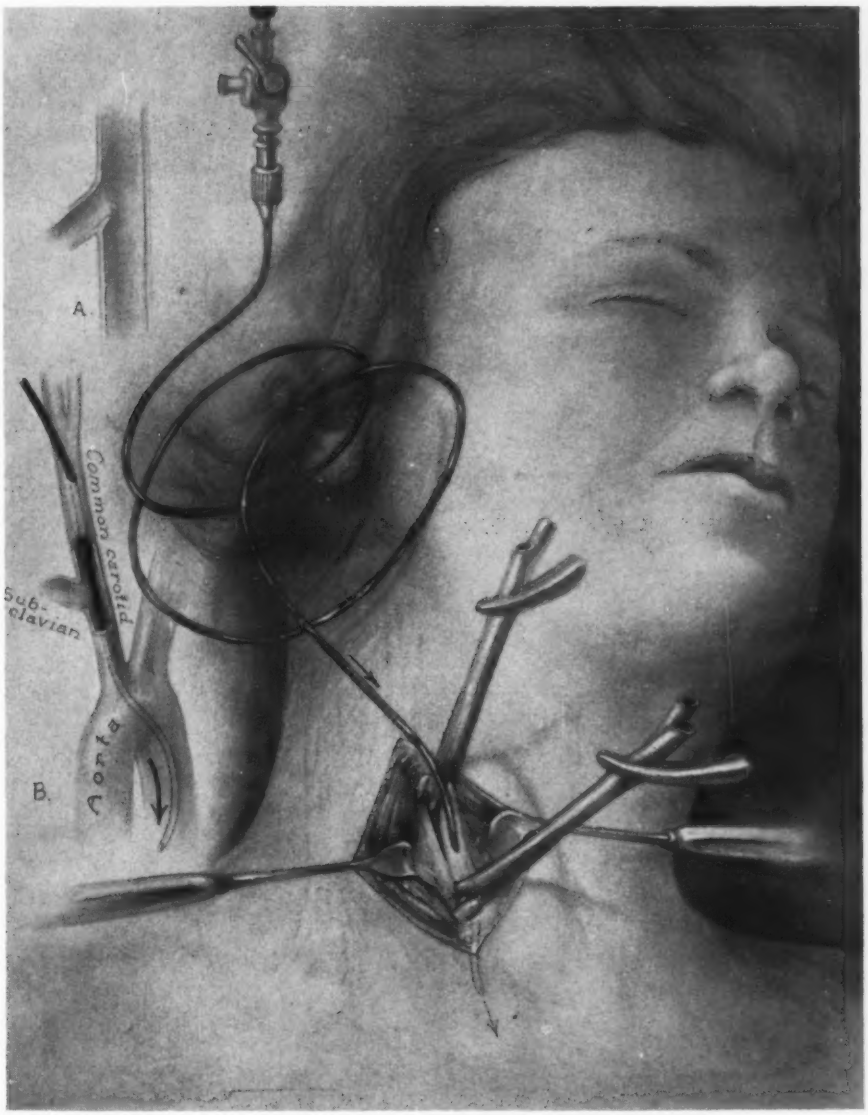

Fig. 1. Exposure of the right carotid artery for insertion of the catheter. Tension on the loops of soft rubber tubing prevents bleeding about the catheter and at the same time does not interfere significantly with the blood flow through the artery. At A, branching from the aorta in the direction of flow. The small valve-like projection on the distal rim of the orifice renders retrograde catheterization difficult. At B, passage of the catheter into the descending aorta.

dark. The catheter is advanced into the aortic arch via the innominate artery. With the curve and tip of the catheter pointing to the left and posteriorly, the catheter is moved rapidly into the artery, the flow of blood and direction of the catheter assisting it along the transverse aortic arch and into the descending aorta (Fig. 1*B* and 2). The tip of the catheter is kept pointing laterally to avoid entering the intercostal branches which arise from the posterior surface of the aorta. These vessels and the lumbar arteries can be catheterized with a No. 9F intracardiac catheter, although a No. 7F or No. 8F may prove easier (Fig. 3).

To enter the celiac artery, the tip of the catheter is pointed anteriorly as it descends to the aortic hiatus at the level of the diaphragm (Fig. 2*D*). Approximately 1 to 1.5 cm. below this point the catheter can be felt entering the celiac artery as indicated by resistance to further progress and confirmed by accentuation in the curve of the catheter (Fig. 2*E*). The injec-

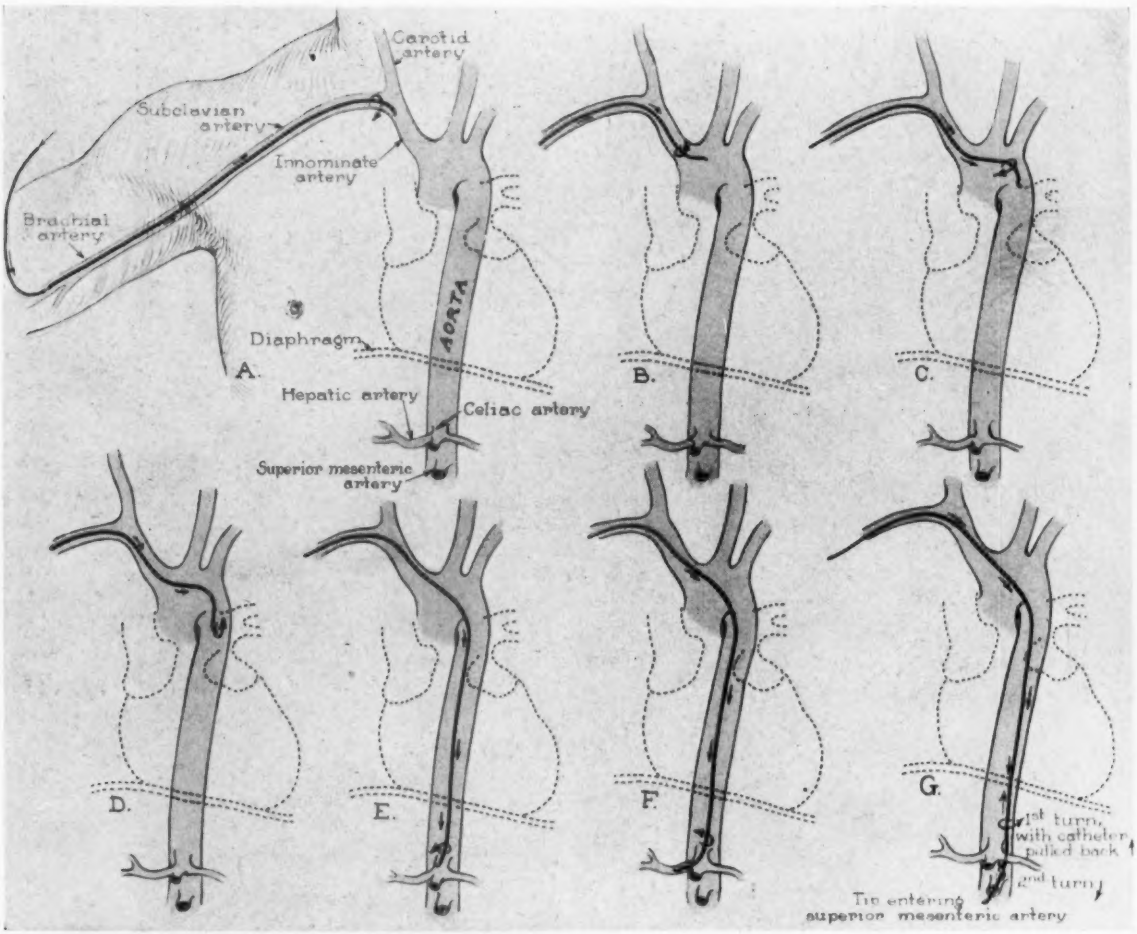

FIG. 2. Arterial catheterization of the celiac and superior mesenteric arteries via the brachial artery. The catheter tip is rotated as depicted under roentgenoscopy. The tip must be guided around the celiac artery and rotated back if entrance into the superior mesenteric artery is desired.

tion of 5 cc. of 70 per cent 3, 5-diiodo-4-pyridone-N-acetic acid diethanolamine (diodrast) visualizes the vascular pattern of the hepatic, left gastric, and splenic arteries and their branches Fig. 4, *A*, *B*, *C*). The hepatic artery may be entered by turning the catheter tip laterally to the right and with slight retraction and advancing of the catheter, it will usually make its way into the hepatic vessel (Fig. 2*F*, 5). Frequently, as slight forward pressure is kept on the catheter in the celiac artery, the catheter tip will make its way into the hepatic artery as it recoils during the rapid injection of

FIG. 3. Diodrast arteriogram of the arterial supply to the diaphragm following catheterization of superior phrenic artery.

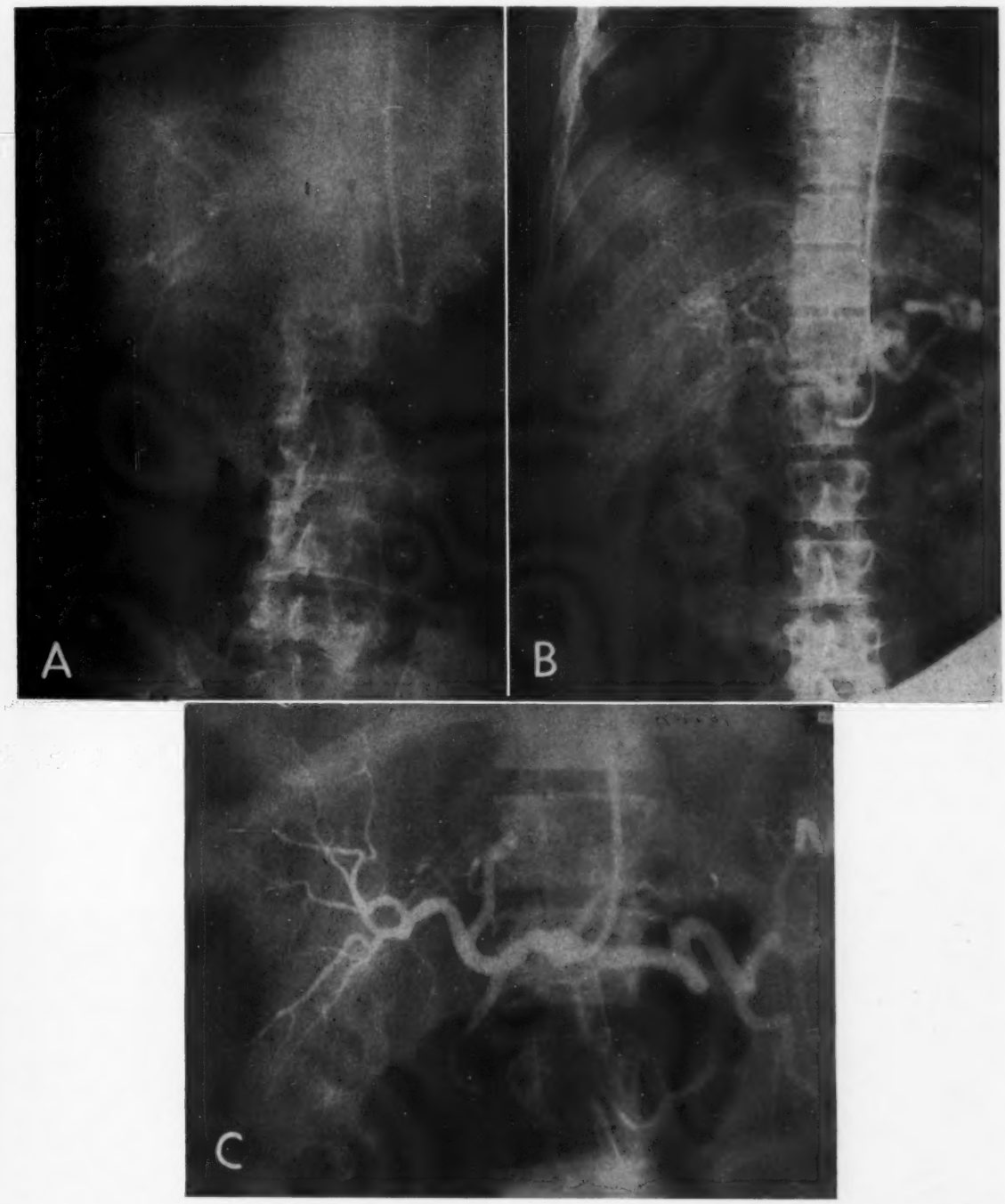

Fig. 4. (*A*) Catheterization of the celiac axis with diodrast visualization of the arterial blood supply of an enlarged liver, spleen, and gastric vessels. The left renal pelvis and both ureters are also seen. (*B*) Catheter in the celiac axis at the junction of the splenic and hepatic arteries. Note extreme tortuosity of the splenic artery. (*C*) Distribution of the hepatic, left gastric, pancreatic, duodenal, and splenic arteries from the celiac axis following diodrast injection.

diodrast or saline. The flow of diodrast through the arteries is rapid so that accurate timing for the roentgenogram is essential if a film of the vascular pattern is desired.

The superior mesenteric, inferior mesenteric, renal (Fig. 6), middle sacral, iliac, hypogastric, and gluteal vessels (Fig. 7) have been similarly catheterized. Indeed, if the catheter tip is not

FIG. 5. Catheter inserted through the celiac axis into the main hepatic artery. The left hepatic artery is displaced to the right by a large intrahepatic mass.

kept pointing anteriorly and laterally, it is difficult to avoid these arteries while the catheter advances inferiorly.

Tumor masses in the neck may prevent satisfactory exposure of the carotid arteries. To reach the carotids, subclavians, and their branches under these circumstances, the brachial, ulnar, and femoral arteries have been employed. The ulnar artery is small and contracts down tightly on catheters larger than No. 6F, making it difficult to manipulate the tip once it reaches the aortic arch and a considerable length of the catheter has been inserted. It is also possible, but difficult, to catheterize one carotid artery from the contralateral side. The femoral approach has proved more satis-

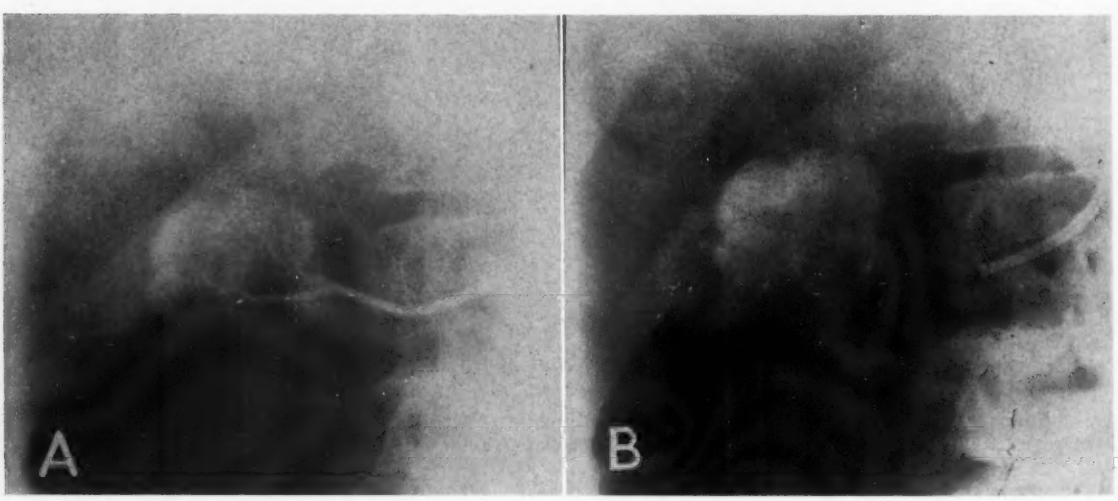

FIG. 6. Catheter in the artery of the inferior pole of the right kidney. (*A*) Catheter in the artery of the superior pole of the kidney. Note interlobular arteries leading to the cortex. (*B*) Ninety seconds after diodrast injection at above site.

factory. By inserting the catheter through either femoral artery and up to the aortic arch, it is possible to catheterize both carotids and subclavians (Fig. 8, *A*, *B*), the internal mammary, thyrocervical axis (Fig. 9, *A*, *B*), and vertebral arteries (Fig. 10, *A*, *B*, *C*). Thirty-five per cent diodrast is used whenever the possibility exists that diodrast may reach the brain directly.

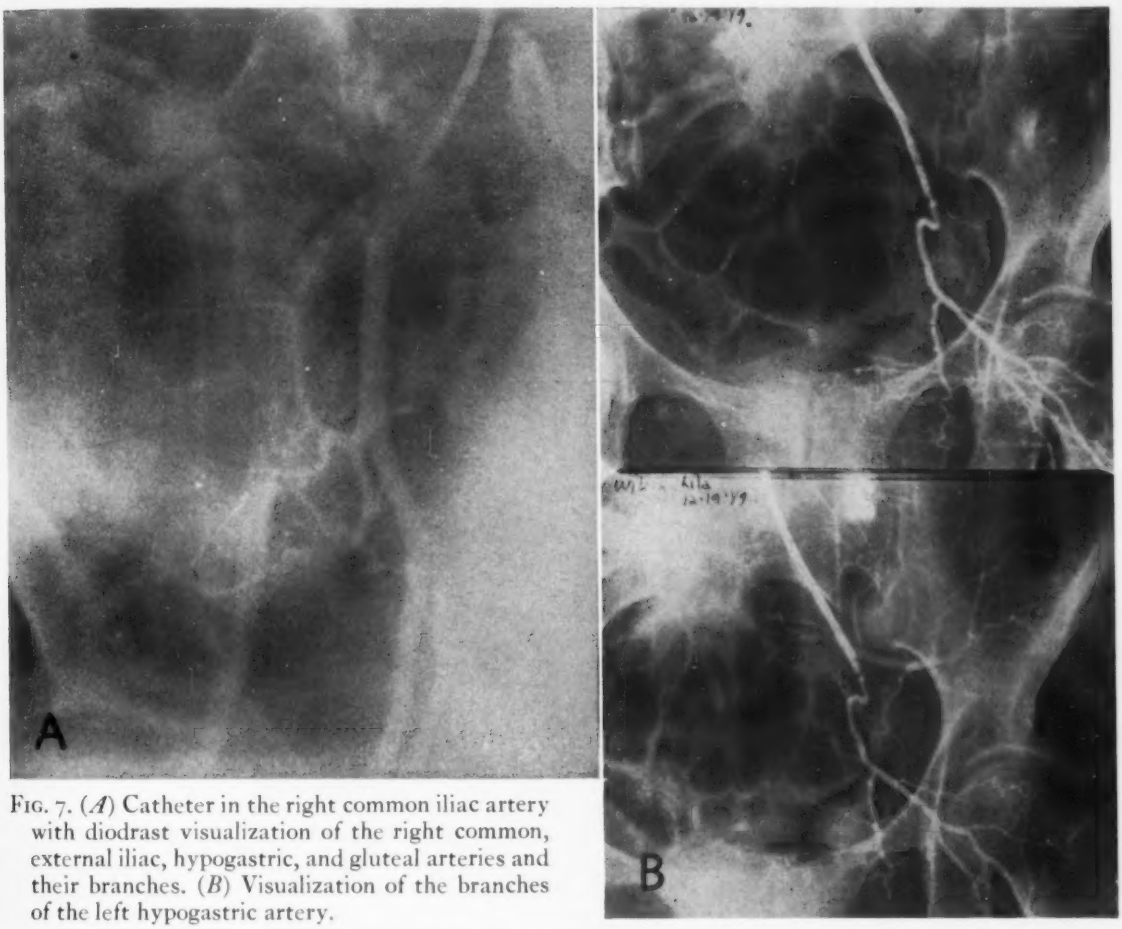

Fig. 7. (*A*) Catheter in the right common iliac artery with diodrast visualization of the right common, external iliac, hypogastric, and gluteal arteries and their branches. (*B*) Visualization of the branches of the left hypogastric artery.

After completion of the procedures with the catheter in place, the catheter is withdrawn under roentgenoscopic control and the arterial incision is closed with arterial silk suture after milking the artery from both ends to remove any thrombi that may be present. The wound is closed in routine fashion.

RESULTS

As given in Table 1, intra-arterial catheterization, visualization of the blood supply of various viscera, was performed on 24 patients. In only 1 case did an attempt at catheterization of the celiac axis fail. In this case the catheter was passed easily to the aortic arch but it was impossible to make the acute turn into the descending aorta from the left subclavian artery. The catheter was passed easily into the ascending aorta and left ventricle. This patient was a male, aged fifty-six, with an aortic insufficiency and aortic aneurysm and it was felt inadvisable to force the catheter by the thin dilated aortic wall.

The photographs (Fig. 3–10) illustrate the pattern of the various regions outlining the smaller as well as the larger arteries. The arterial pattern of the hepatic, splenic, gastric and renal vessels were clearly visualized. As seen in Figure 4*B*, the tortuosity

TABLE I

ARTERIAL CATHETERIZATIONS

Patient	Sex Age	Diagnosis	Catheter Introduced in Artery	Artery Reached	Diodrast		Arteries or Viscera Visualized	Complications or Comments
					Conc. per cent	Vol. cc.		
T.H.	M34	Adenocarcinoma of lung	Right carotid	Aortic arch	0	0	—	None
C.B.	M63	Cancer of kidney	Right carotid	Aortic arch	0	0	—	None
G.B.	M48	Adenocarcinoma of kidney	(a) Right femoral	Aorta	0	0	—	None
			(b) Left carotid	(a) Celiac (b) Left renal	70	30	Branches of celiac	None
H.H.	M42	Unspecified malignancy of presacral area and aortic nodes	Right carotid	(a) Branches of celiac axis (b) Lumbar vessels	70	45	Superior mesenteric. Celiac axis	None
A.P.	M58	Mycosis fungoides	Right carotid	Aorta	70	55	Liver well outlined. Branches of celiac artery	Wound infection. Aneurysm. Left hemiplegia
E.U.	M31	Teratoma of testes	(a) Right carotid	Right hypogastric	70	50	Right kidney. Right hypogastric artery	None
			(b) Left femoral	(a) Right mammary (b) Transverse scapular	70	30	Right internal mammary. Right thyrocervical axis	None
C.L.	M36	Adenocarcinoma of stomach	Right common carotid	(a) Right renal (b) Celiac axis	70	50	Branches of celiac artery. Right kidney	None
R.L.	M53	Malignant melanoma	Left brachial	(a) Left renal (b) Celiac axis (c) Hepatic	70	80	Branches of celiac axis and renals	None
G.M.	F43	Epidermoid carcinoma of nasopharynx with metastases to neck	(a) Left ulnar	—	35	50	Right common and internal carotid	Ulnar artery too small to manipulate catheter into external carotid
			(b) Left femoral artery	Right common carotid	35	30	Right internal carotid	Could not enter external carotid artery
			(c) Right common carotid	—	0	0	—	External carotid artery could not be entered
A.R.	M29	Hodgkin's disease with liver involvement	Right common carotid	(a) Right renal (b) Celiac	70	50	Right kidney Hepatic artery network.	None
I.S.	M54	Carcinoma of unknown site, metastatic to liver	Right carotid	Celiac	70	75	Hepatic network and metastases	None
T.F.	F8	Hemangioendotheliosarcoma of left eyelid	Left superficial femoral	(a) Left common carotid (b) Left internal carotid (c) Left thyrocervical axis	35	30	Left common carotid. Left internal carotid. Left thyrocervical axis	None

TABLE I—*continued*

Patient	Sex Age	Diagnosis	Catheter Introduced in Artery	Artery Reached	Diodrast		Arteries or Viscera Visualized	Complications or Comments
					Conc. per cent	Vol. cc.		
R.F.	M65	Carcinoma of larynx, metastatic to right neck	Right common carotid	Right external carotid	35	11	Right internal carotid	Developed left-sided paralysis due to mass occluding right internal carotid during procedure
R.G.	M46	Adenocarcinoma of colon, metastatic	Right common carotid	(a) Celiac (b) Splenic	70	35	Branches of celiac axis	None
C.C.	M59	Adenocarcinoma of sigmoid colon with metastases	Right common carotid	(a) Celiac (b) Hepatic	70	35	Branches of hepatic artery	None
L.V.Z.	F14 mo.	Retroperitoneal sarcoma	Left femoral artery	Aorta	0	0	—	None
M.D.	M47	Recurrent epidermoid carcinoma of face	Right common carotid	Right external carotid	0	0	Fluorescein showed poor vascularity	None
T.M.	M47	Cancer of pancreas	Right carotid	Celiac axis	50	50	Branches of celiac	None
L.W.	F39	Metastatic squamous cell carcinoma of cervix	Right common carotid	Left hypogastric	70	35	Left hypogastric vessels	Developed left hemiplegia. Right common carotid occluded
G.Z.	M8	Lymphoepithelioma, right tonsillar fossa	Right external carotid	Right external carotid	0	0	External carotid and tumor with fluorescein	Tumor area fluoresced brightly
F.F.	M55	Hodgkin's disease	Left brachial	(a) Celiac (b) Hepatic	70	50	Branches of hepatic	None
F.R.	F41	Lymphosarcoma	Right brachial	Hepatic	70	75	Hepatic vessels. Splenic vessels	None
P.B.	M32	Lymphosarcoma	Right brachial	Aortic arch	50	40	Lumbar vessels	None
G.J.	M56	Metastatic adenocarcinoma. Aortic aneurysm. Aortic insufficiency	Left brachial	Aortic arch	0	0	—	Thrombosis in left brachial artery postoperatively

of the splenic artery may be marked. Increased vascularity about neoplasms in the liver and in other areas was noted in 4 of 5 patients with metastases of the liver. In the fifth patient the distortion of the vessels was apparent (Fig. 5). The eventual value of this method for the visualization of visceral neoplasms must await further investigation on larger numbers of patients.

COMPLICATIONS

Four complications have been encountered. There was a wound infection in 1 case (A. P., aged fifty-eight) with subsequent hemorrhage three weeks after catheterization. In this case the exposure of the carotid artery had to be performed through a large lesion of mycosis fungoides which, despite rigorous cleansing, probably was not completely sterile. The erosion in the artery was sutured, but was followed within thirty-six hours by a left hemiplegia, with later recovery of motion in the face and lower extremity. Approximately eight weeks later hemorrhage again ensued and the carotid was ligated without significant change in the patient.

The second complication during the pro-

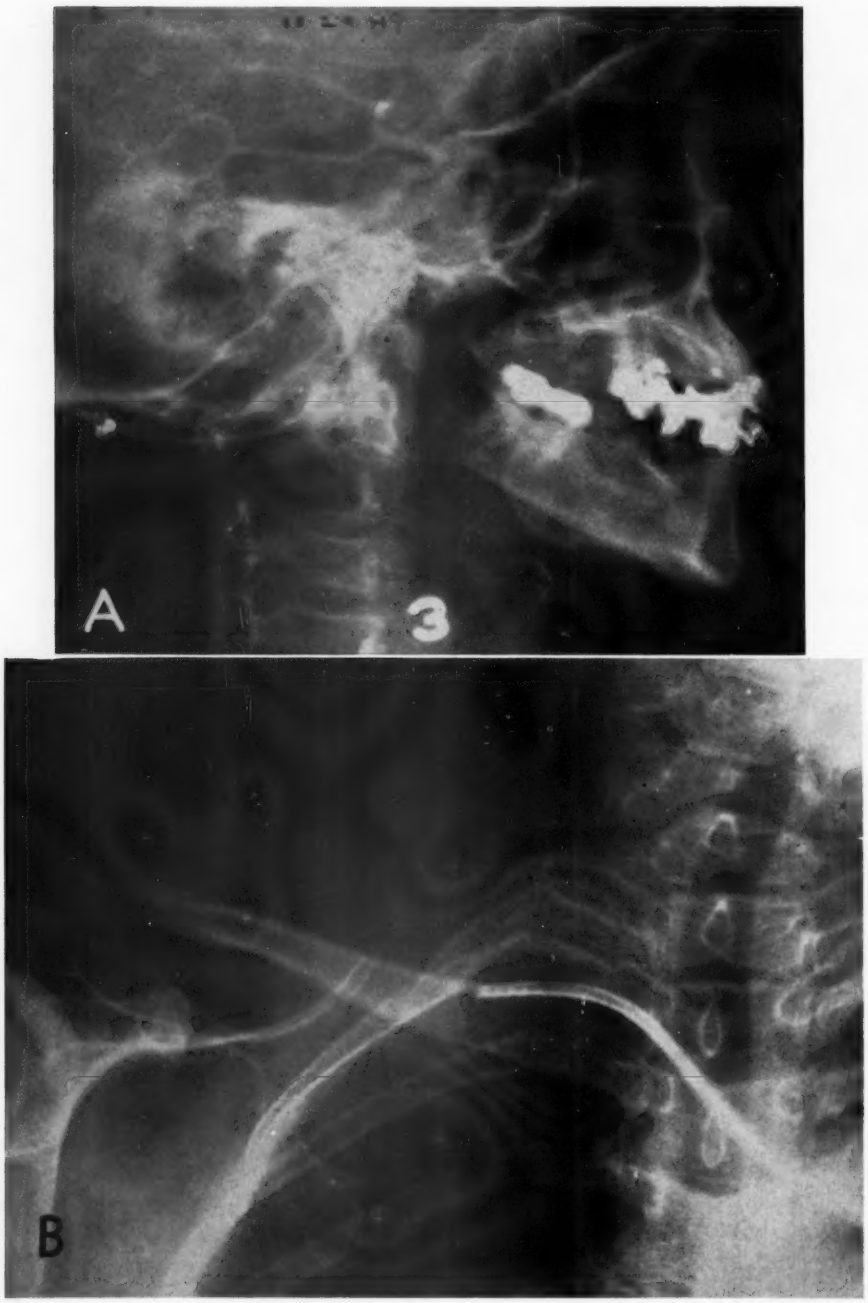

Fig. 8. (*A*) Catheterization of the internal carotid artery via the femoral artery and arteriogram of the brain following diodrast injection. Complete filling of the cerebral vessels was not obtained since the primary purpose of this roentgenogram was to show the catheter tip (at the bottom of the figure) in a position to do cerebral angiography without direct attack upon the carotid arteries. The catheter can also be placed in the carotid arteries from either brachial artery. (*B*) Catheter in the right subclavian artery via the left femoral artery.

cedure occurred in a male, aged sixty-five (R. F.) with carcinoma of the larynx, metastatic to the neck with a hypertension of 170/110, arteriosclerotic heart disease, and chronic nephritis (non-protein nitrogen 59 mg. per cent). The patient developed a left hemiplegia five minutes after the procedure started and after the injection of

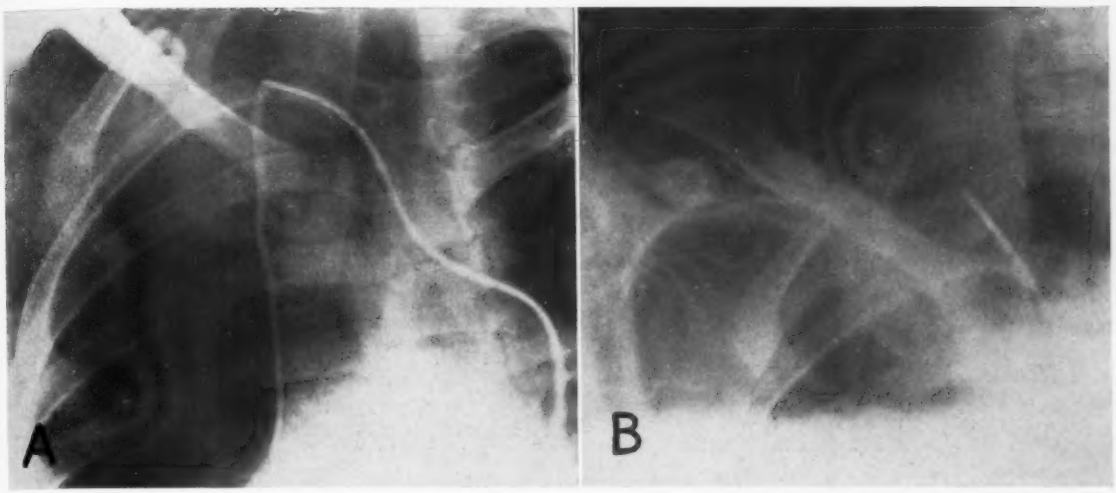

Fig. 9. (*A*) Catheterization of the right internal mammary artery via the right femoral artery. Note catheter passing retrograde into the arch of the aorta, thence into the innominate, and out the subclavian to the orifice of the right internal mammary artery. Note the small intercostal arteries and the large tumor mass in the lower right corner. (*B*) Catheter tip in the right thyrocervical axis with visualization by diodrast of its branches. Previous surgery in the right neck is responsible for the lack of vascular pattern in the upper and medial areas.

only 11 cc. of 35 per cent diodrast. He died four days later. The right cerebral hemisphere was found to be infarcted, probably due to the marked arteriosclerosis of the right carotid artery together with compression of the artery by the tumor mass, as the head was moved to the left during the procedure, and perhaps aided by arterial spasm from the diodrast.

In a third case (L. W.) the physician holding the rubber bands about the artery became confused in the dark of the roentgenoscopic room and somehow switched the clamps so that tension was exerted downward on the upper tubing and upward on the lower tubing, resulting in twisting the artery into a knot and completely shutting off the blood flow through the right common carotid. Complete left hemiplegia appeared twelve hours later.

The fourth complication occurred in a moribund male, aged fifty-six, with marked arteriosclerosis, syphilitic aortitis, aortic insufficiency and widespread metastatic adenocarcinoma. The blood pressure in the right arm was 90/0 and 160/70 in the left

Fig. 10. (*A*) Catheterization of the left vertebral artery in an eight year old girl with a large hemangioendothelial sarcoma of the left head and neck. Note reflux of diodrast into the left subclavian artery and its branches. (*B*) Distribution of the left external carotid artery. (*C*) Catheterization of the left internal carotid artery. Note vascular pattern of the tumor in all three films.

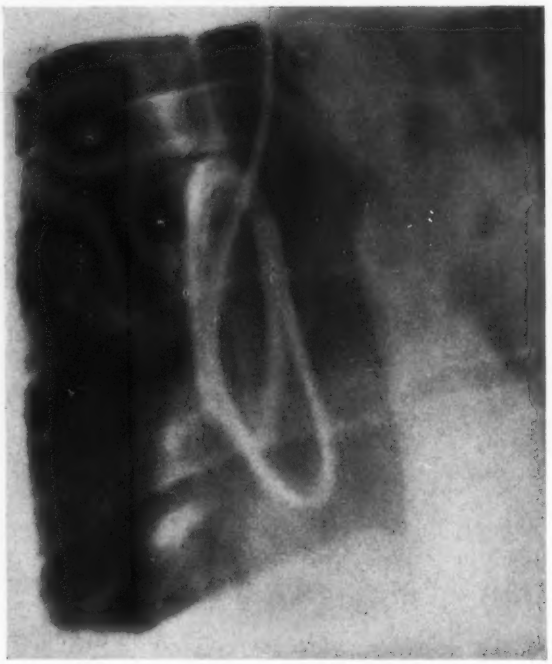

Fig. 11. Coiled catheter in ascending aorta (oblique view).

The catheter was inserted into the left brachial artery at the mid-humeral level. Twelve hours later the forearm and hand were cyanotic, cold and cadaveric. The patient continued to fail progressively and died forty-eight hours after nitrogen mustard was administered into the aortic arch and a thrombus was found just above the cut-down site.

Early in our experience, on one occasion the catheter was inserted and passed onward, because of the lack of resistance, before the roentgenoscope was ready. The lack of resistance was thought to indicate passage into the descending aorta, but instead the catheter became coiled up in the ascending aorta. Fortunately, by slow withdrawal it was uncoiled without knotting (Fig. 11).

In patients with a tortuous aortic arch, twisting the catheter for positioning the tip in abdominal visceral arteries may cause the middle of the catheter to backlash into the ascending aorta (Fig. 12). Careful withdrawal of the catheter until it straightens will permit the procedure to be resumed.

DISCUSSION

The technique of intra-arterial catheterization has proved to be a feasible procedure. However, it must be undertaken with a calculated risk. When the carotids are to be used for the catheterization in the presence of arteriosclerosis, increasingly prolonged compression of the carotid artery prior to the procedure is advisable, particularly when the danger of occlusion of the carotid exists due to cervical masses, or in previously irradiated areas. Periodic progressive compression of the carotid for ten minutes three times each day should be attained without symptoms as a prophylactic against hemiplegia.[14] Full range of motion of the head laterally should also be tested and any symptoms noted. The development of hemiplegia is absent if the brachial arteries are used, although the manipulation of the catheter is more difficult.

The injection of a 70 per cent diodrast solution usually, but not always, causes the

Fig. 12. Backlash of catheter into ascending aorta during rotation of the catheter in a patient with a tortuous aortic arch.

patients to complain of a burning sensation along the course of the vessels with somatic reference. The position of the catheter may often be confirmed in this manner.

While four serious complications in a group of 24 patients would appear to give a high incidence, it is not prohibitively high considering the initial effort in this direction, mostly on critically ill patients with far advanced neoplastic illnesses. The complications of wound infection (Case I) and surgical error (Case III) are avoidable and have been corrected. From our further experience it is now almost certain that the complication in Case II was in all likelihood due to a diodrast reaction which together with the marked arteriosclerosis and large metastatic tumor was sufficient to cause cerebral anoxia. The fourth complication occurred before we instituted the milking of the artery from both ends to remove any thrombi that may have occurred during the procedure. Since that time no further complications of this sort have been noted.

New techniques encounter difficulties until they are perfected. Since the complications noted were all amenable to improvement, as has been shown in the later catheterizations, it would appear that this procedure has some value for the purpose stated.

SUMMARY

1. A clinical technique of arterial catheterization of viscera in man has been developed.

2. The celiac axis, hepatic, renal, phrenic, lumbar, superior and inferior mesenteric, and iliac arteries have been entered by means of an intra-arterial catheter introduced from the carotid and brachial arteries. The carotids, subclavian, internal mammary, vertebral, and thyrocervical trunk have been catheterized by way of the femoral arteries.

3. The arterial patterns of the liver, spleen, stomach, kidney and diaphragm have been visualized roentgenographically.

4. The complications encountered and the hazards of the procedure have been discussed.

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CARCINOID OF THE DUODENUM*

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A ROUND or lobulated defect in a barium-filled first portion of the duodenum is usually produced by a benign tumor, most frequently adenoma, papilloma, leiomyoma, or lipoma. This concept justifiably stems from the early reports of Carman,[3] Camp,[2] Golden,[5] and Waters.[11] Occasionally, a similar defect is produced by a pancreatic rest, a prolapsed gastric polyp or, infrequently, by prolapsed gastric mucosa. The fact that a carcinoid of the duodenum may be similar roentgenologically has not been stressed.

In 1946, 3 patients were seen with single rounded defects in the first portion of the duodenum. Each of these was a carcinoid. The 3 cases are recorded in this report.

CASE REPORTS

Case 1. A sixty-four year old steelworker was first seen at the Cleveland Clinic on April 9, 1946, complaining of pain in the stomach. The pain had been intermittent in character for two years. It began one hour after meals and was relieved by milk and antacids. There was no history of hematemesis or melena.

The systemic review and past history were non-contributory. There were no positive physical findings.

A gastrointestinal roentgen examination on April 11 demonstrated a tortuous gastric antrum through which active peristaltic waves passed. No ulcer or ulcer scar was demonstrated. Along the inferior margin of the duodenal bulb there was a polypoid filling defect (Fig. 1*A*). On April 12, a gastroscopic examination showed normal mucosa with no gastric polyps. There was shortening of the posterior wall of the stomach with posterior retraction of the pylorus. Gastritis of the deeper layers of the stomach wall was considered a possible cause of the shortening.

On May 2, 1946, the roentgenoscopic examination was repeated, and the same polypoid defect was demonstrated in the duodenal bulb (Fig. 1*B*).

On May 24, during exploration of the duodenum,* a polyp-like tumor with narrow base and short pedicle was found and removed from the posterior-inferior wall of the duodenum just beyond the pylorus.

Pathology. The specimen consisted of a polypoid structure 12 by 15 by 18 mm. The surface was slightly granular and pinkish in color. On section, the tissue was found to be moderately firm and yellow.

Microscopic examination revealed a tumor mass infiltrating the mucosa and submucosa of the duodenum and formed by irregular masses of epithelial-like cells, arranged in columns or cords, adjoined by capillaries (Fig. 2). The neoplasm was not encapsulated, irregularly infiltrated the mucosa and the submucosa, and extended to but not into the muscularis. Despite the absence of capsule the lesion was somewhat circumscribed and was bounded by normal duodenal tissue. Cells forming the neoplasm showed indefinite boundaries, except for the margins of the columns. The cytoplasm was pale staining and homogeneous, and contained well differentiated, oval or round nuclei in linear arrangement, numbering one to three in depth along the column. In a few areas cytoplasmic margins were apparent, and in these the cells were of columnar shape, and perpendicular to the axis of the cord. The cells varied up to 25 microns in greatest height; nuclei presented a uniformly coarsely granular chromatin and measured from 7 to 10 microns. No mitoses were present and there were no areas of necrosis. The duodenal glands were of noticeably reduced number in the regions of greatest infiltration by neoplasm. However, in all instances the duodenal surface was intact without ulceration, even though covered by a single layer of columnar epithelium.

Stains for argentaffin granules were negative.

The postoperative course was uneventful, and the patient was discharged on June 4, 1946.

He was next seen on August 20, 1948, having characteristic symptoms of a peptic ulcer. He

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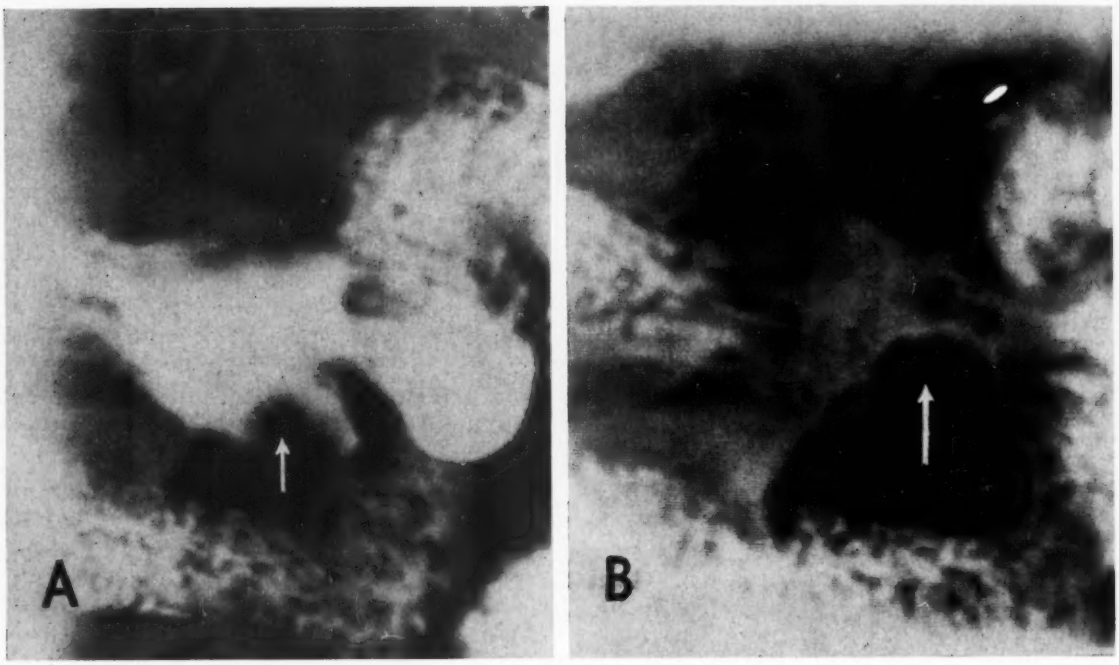

Fig. 1. Case 1. (*A*) Spot roentgenogram showing rounded defect along inferior margin of duodenal bulb near base. (*B*) Spot roentgenogram made approximately one month after (*A*), also showing a sharply demarcated rounded filling defect in same location in duodenal bulb.

admitted excessive alcoholic consumption for one year.

Roentgenographic examination the same day revealed a large gastric ulcer along the lesser curvature of the pars media close to the posterior wall. The duodenal bulb was slightly deformed but there was no evidence of tumor infiltration or recurrent polyp.

On September 8, 1948, a subtotal gastric resection was performed to remove a large benign gastric ulcer (4 by 2.5 cm.) which was eroding into the pancreas. The duodenum was examined and no recurrent lesion was found.

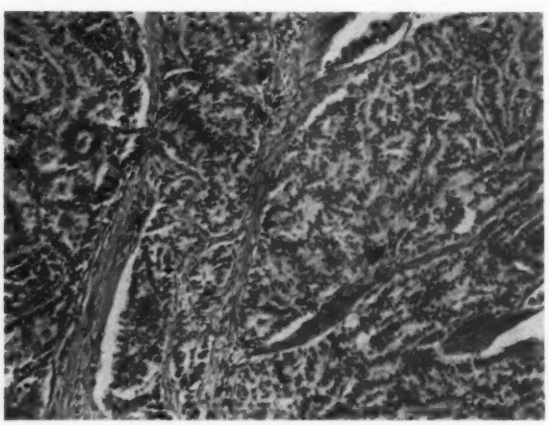

Fig. 2. Case 1. Photomicrograph of section through area of submucosal infiltration showing uniform epithelial cells in columns separated by capillaries and fibrous trabeculae. Nuclei are in linear arrangement and cell margins indistinct (×70).

The postoperative course was stormy and an emergency exploratory laparotomy was done two days later. The abdomen was filled with reddish fluid and gas due to a mesenteric thrombosis and gangrene of the terminal ileum and ascending colon. A right colectomy with end ileostomy and transverse colostomy was performed. The patient died ten hours later. An autopsy was not performed.

Case II. A sixty-three year old retired white man was first seen at the Cleveland Clinic on September 4, 1946. His principal complaint was poor vision. His vision had been blurred for thirteen years, but in recent months it had become rapidly worse until he could no longer read. There was a history of penile chancre at the age of twenty. He had had no antisyphilitic therapy. In 1933, during a routine examination for failing vision he was informed of his positive serologic reaction, and had received alternating intravenous and intramuscular injections for about six months. His last serologic test in January, 1946, was negative.

He had been married for thirty-seven years

and had 4 living adult children. His wife had no known miscarriages. His only previous operation was a bilateral high saphenous vein ligation.

Ophthalmologic examination revealed diffuse lens changes with bilateral marked pigmentary degeneration of the retina. In addition, there was bilateral chorioretinitis. A urologic consultation revealed Grade 1 prostatic hypertrophy. While evaluating further syphilitic therapy, the consultant noticed the patient was slightly jaundiced. For this reason he was asked to return to the Department of Gastroenterology for further study on October 31, 1946. He described a six year history of gaseous dyspepsia and heart burn. He had had frequent attacks relieved by sodium bicarbonate and occurring one to three hours after meals. There was no other distress between meals. In the past year the pain radiated to either shoulder or to the lower abdomen and occasionally had been accompanied by chills. He had required hypodermics for relief of pain ten or twelve times in the past year. During the attacks he noticed his urine had been dark; he had not noticed the color of his stools. In the past four months he had lost 25 pounds in weight.

His physical examination was normal except for the previously described eye changes and for stasis dermatitis of both legs. Hemorrhoids of a mixed type were present.

Wassermann and Kahn tests of the blood were negative. The spinal fluid Kahn reaction was negative and the total spinal fluid protein was 33 mg. per 100 cc. The urine was positive for urobilinogen and bile and there were a few hyaline and granular casts. Stool examination was negative. There were 4,800,000 red cells per cu. mm. and the hemoglobin was 13.5 gm. The white blood cell count was 9,300, with normal differential. The icterus index was 15. A blood sugar test was 88 mg. per cent and a blood urea 36 mg. per cent. A bromsulfalein liver function test demonstrated 32 per cent retention in thirty minutes. The prothrombin time was normal. A cephalin flocculation reaction was 1 plus.

The gallbladder did not visualize after two doses of priodax (9 gm.) and a moderate-sized gallbladder calculus was noticeable. On roentgenographic examination the prepyloric portion of the stomach was somewhat narrow and elongated. A rounded defect was visible in the base of the duodenal bulb (Fig. 3). A diagnosis

Fig. 3. Case 11. Spot roentgenogram of partially empty duodenal bulb showing round filling defect in central portion of bulb near base.

of duodenal polyp and benign hypertrophy of the pylorus was considered.

Cholecystectomy and exploration of the common duct and stomach were recommended by the surgical consultant. On November 11, 1946, the gallbladder containing one large and one small stone was excised. The common duct was enormously dilated in its proximal portion but was normal in size adjacent to the duodenum. No stones were found in the common duct but there was definite resistance at the ampulla. The duodenum was opened and a pedunculated tumor was immediately perceived in the first portion. The tumor, along with its pedicle and base, was excised.* Several biopsy specimens were taken from the ampulla of Vater and the histopathologic examination showed only chronic inflammation. There was no adequate explanation for the dilatation of the common duct (T-tube was left in the common duct). The stomach was grossly normal. The postoperative course was uneventful. The T-tube was removed on the eighteenth postoperative day and replaced by a catheter. The catheter was removed five days later.

The patient was last seen on December 4, 1946.

Pathology. The major portion of the specimen was an ovoid, broad based, polypoid mass,

* Operation performed by Dr. George Crile, Jr.

16 by 14 by 9 mm., with a glistening and somewhat smooth convex surface and adjoined by a narrow zone of mucous membrane (Fig. 4). The tissue was firm, and when sectioned was slightly lobulated, cut with moderate resistance, and presented a slightly bulging, yellowish surface. Several separate tissue fragments, 3 to 12 mm. in diameter, pliable, pink and white, were also received.

Fig. 4. Case II. Gross specimen showing broad based polypoid mass covered by mucosa.

On microscopic examination the tumor was found to be comprised of solid islands and cords of uniform small cells, with a moderate amount of pink-staining and homogeneous cytoplasm (Fig. 5). It showed infiltration of mucosa and submucosa, but no infiltration of muscularis. The solid architecture was somewhat broken up by the presence of capillary vessels, some engorged, separating the small, uniform cells which at times were oval or polyhedral and at other times of indefinite shape, occurring as syncytial masses. Where measurable, the cells varied from 7 to 10 microns in diameter. The nuclei were round or oval, well differentiated, with uniform, coarsely granular chromatin, and measured 5 microns. No mitoses were evident, and there were no zones of necrosis. In the region of involvement of the mucosa, the duodenal glands were reduced in number, but there was no erosion of the surface. In all locations at least a single layer of columnar duodenal epithelium was present superficially. Brunner's glands were absent in the region of involvement. Several islands of neoplasm were present quite close to the deep line of excision, but did not appear to reach the latter. Separate tissue fragments revealed mucous membrane, smooth muscle, and contained glandular elements similar to those of biliary tract.

Case III. A housewife, aged seventy, was treated with radon (intravaginal) on October 8, 1946, and November 12, 1946, for a poorly differentiated squamous cell carcinoma of the cervical stump. The carcinoma invaded the entire cervical stump and extended into the vaginal fornices.

She returned on June 24, 1947, with her cervical lesion apparently controlled. She complained of a dull tearing pain in the epigastrium radiating into the back. The attacks occurred three or four times weekly and were relieved by morphine. She had experienced considerable gaseous belching and flatus but no jaundice or clay colored stools.

The patient had one cystic ovary removed and a uterine suspension in 1911. In 1916 the remaining ovary, both fallopian tubes, the uterus and appendix were removed, and a diagnosis of tubal pregnancy was confirmed. In 1944 a cholecystostomy was done for cholelithiasis.

The current physical examination was not significant except for elevated blood pressure. The vagina was shallow and somewhat constricted but no residual tumor tissue was identified.

Two 4.5 gm. doses of priodax were ingested on successive days but the gallbladder was still not visualized. No gallbladder calculi could be seen on plain roentgenograms of that area. Roentgenoscopically the esophagus and stomach were normal. A rounded filling defect 2 cm. in diameter was seen in the base of the duodenal bulb (Fig. 6). The appearance suggested a primary benign tumor in the first portion of the duodenum. Roentgenograms of the dorsal and lumbar spine revealed nothing significant.

On June 30, 1947, the gallbladder was re-

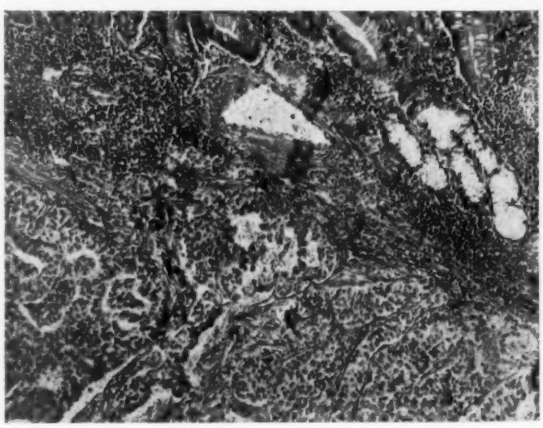

Fig. 5. Case II. Columns of uniform epithelial cells in submucosa and interrupting muscularis mucosa (×100).

moved; it was contracted, small, and contained gravel. An incision was made in the duodenum immediately distal to the pyloric ring and a carcinoid was excised along with a wedge-shaped piece of mucosa.* The tumor, located in the posterior-superior wall of the duodenum, was hard and freely movable.

Pathology. The tumor consisted of a polypoid tissue mass 30 by 20 by 20 mm., the convex surface of which was smooth, pale pink and appeared to be covered by mucosa. The cut surfaces were yellowish-brown, finely granular and of firm consistence. The sectioned surface was finely lobulated with white strands of tissue separating the lobulations.

On microscopic examination the tumor was found to infiltrate the mucosa in the central portion of the specimen as well as the submucosa, and to a slight extent the muscularis. The neoplasm occurred as solid masses broken by capillary vessels and accompanying stroma (Fig. 7), as irregular columns, and as small cell groups in dense connective tissue. The solid masses of cells occurred as groups, 5 to 15 cells in thickness, adjoined by capillaries with a small amount of stroma. The nuclei were evenly dispersed and the indistinct cytoplasmic margins produced an appearance of a syncytial arrangement in many areas. Judged by distribution of the nuclei, cell units appeared to be approximately 8 microns in diameter; the nuclei were round or slightly oval, uniform, 5 to 6 microns in diameter, slightly vesicular, but with rather evenly distributed granular chromatin. No mitoses were apparent. There were no zones of necrosis. In the region of infiltration, the mucosa showed a definite reduction in the number of normal glandular elements remaining, but the surface was covered by intact duodenal epithelium although in some regions this was flattened and separated from the underlying neoplasm by only a small amount of tunica propria. There were no areas of ulceration. Brunner's glands were absent in the region of involvement. Islands of neoplasm appeared to be present in all portions of the sections, except for the muscularis at the margins.

Fig. 6. Case III. Roentgenogram made in right anterior oblique position showing round sharply marginated filling defect in base of duodenal bulb. There is associated pylorospasm.

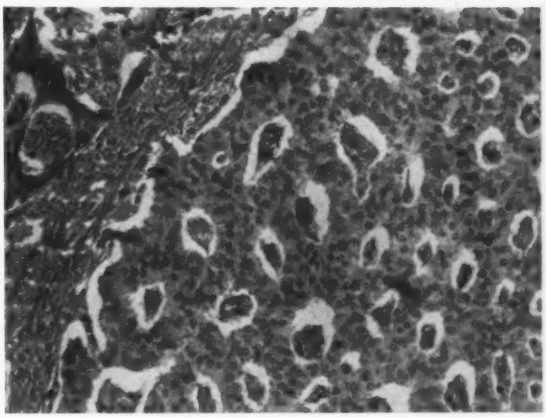

Fig. 7. Case III. Uniform epithelial cells with indistinct cell margins and arranged in solid masses interrupted by evenly distributed capillaries.

The patient was discharged on July 13, 1947, and was not observed until May 26, 1948. At this time her symptoms suggested intermittent large bowel obstruction. A series of gastrointestinal roentgenograms was begun on May 26, 1948. The esophagus and stomach were found to be normal and the duodenal bulb showed no evidence of recurrent tumor. The colon examination showed a polypoid defect at the junction of the sigmoid and descending colon.

The patient was instructed to return within several weeks for re-evaluation but she did not return until September 3, 1948. At this time she had a complete large bowel obstruction, and a cecostomy was performed the next day. A barium enema examination on September 13,

* Operation performed by the late Dr. Thomas E. Jones.

demonstrated a complete obstruction at the site of polypoid growth in the sigmoid colon. On September 16, an obstructive resection of the sigmoid was carried out, and a moderately differentiated annular adenocarcinoma was excised. Microscopic examination showed slight extension of the growth into surrounding fat. There was no neoplasm in four nodes. When the spur clamp was applied on September 22, a small papillomatous polyp was discovered and removed from the distal sigmoid loop.

On December 7, 1948, the colostomy was closed. On discharge from the hospital on December 16, the patient's vagina was normal except for shortening and the cervix was soft and well epithelialized. The fornices were free and flexible.

On September 8, 1949, the family physician stated that the patient appeared to be in good condition.

DISCUSSION

It is difficult to determine the incidence of carcinoid in the duodenum. Ariel,[1] in 1939, reviewing 111 carcinoids of the small intestine recorded since 1930 lists only 5 in the duodenum. Porter and Whelan[9] in 1939 reporting a total of 84 carcinoids, 9 of which were in the small intestine, found only 1 in the duodenum. Ritchie and Stafford[10] in 1944 record only 1 duodenal carcinoid in their series of 9 of these tumors occurring in the small intestine. Pearson and Fitzgerald,[8] in 1949, included in their report 31 non-appendiceal carcinoids, only 1 of which occurred in the duodenum. Thus approximately 8 have been reported so far in this portion of the intestine.

Pathology. In all 3 instances the biopsy specimens presented the problem of carcinoma as differentiated from carcinoid. A firm consistence of the gross specimen without evident boundary was compatible with an infiltrating neoplasm and the granular surface apparent in one, suggested that this was epithelium. However, there was no ulceration in the mucosal aspect and no areas of necrosis were present on the cut surface, which also had a tendency to bulge slightly rather than retain a flat aspect, and was of yellowish tinge, rather than a translucent gray or white. The microscopic differentiation of carcinoma in Cases II and III was made obvious by frozen section examination at the time of operation. The cells occured as uniform units without areas of necrosis, despite their infiltrating character.

The features of gross examination, which serve to differentiate this neoplasm from true carcinoma, might not be so obvious when the pathologist is confronted by a neoplasm which has been reported roentgenologically as a polyp and which the surgeon finds to be an infiltrating neoplasm with all the firmness of true carcinoma. In this respect, the absence of true ulceration is of importance, although lymphoblastoma of the mucous membrane of the duodenum might present such an external appearance. However, with careful inspection of the gross specimen and microscopic frozen section examination, there should be no error in diagnosis. The importance of frozen section examination in identifying these tumors at the time of operation is to be stressed. The following points which served to differentiate these 3 tumors from carcinoma are emphasized: (1) a polypoid mass without mucosal ulceration, (2) a slightly bulging, often yellowish cut surface, (3) absence of necrosis, (4) uniform, small, epithelial-like cells in solid masses, cords or bands broken by capillaries, with a small amount of connective tissue stroma, (5) inconspicuous mitotic activity and an absence of atypical mitoses, (6) an intact though often thinned and distorted mucosal epithelium over the neoplasm.

In 2 instances fixation was such as to make it possible to attempt the demonstration of argentaffin granules, but in neither of the specimens could these be found. The pathologic diagnosis therefore had to be based on morphologic considerations alone.

Gross Appearance. Though each of these 3 carcinoids of the duodenum was of polypoid appearance, no emphasis or particular mention is made of this feature in precedent reports which include cases of these tumors in this site. Polypoid forms are occasionally described in other portions of the gastrointestinal tract though the configuration is

usually that of an infiltrating neoplasm, sessile rather than polypoid, and producing symptoms by constriction and kinking of the bowel, rather than by obstruction by an intraluminal mass.

Microscopic Appearance. These duodenal carcinoids differ in no way from those in other locations. In the 2 instances in this group in which tissue was available properly fixed for their demonstration no argentaffin granules could be found. However, this is also true of some of these tumors in other portions of the intestinal tract, and cannot be regarded as a characteristic attributable to location.

Terminology. The name "carcinoid" was given these neoplasms by Oberndorfer[6] in 1907; the term "argentaffinoma," indicating origin from the argentaffin cells of appendix or intestine having been applied later. The designation "carcinoid" has been used throughout this report even though it is recognized that it should be dropped from usage as soon as a more logical term may be devised. It is descriptive of the neoplasm, yet neither implies an origin which in this instance is not definitely known nor does it indicate the presence of a granulation which cannot be demonstrated.

Association with other Malignant Tumors. One patient (Case III) is of unusual interest in that she first developed a carcinoma of the cervix before the carcinoid in the duodenum became evident, and returned later for removal of an adenocarcinoma of the sigmoid. Due to the small number of cases reported there is no precedent for any positive statement regarding the association of carcinoid of the duodenum and other malignant tumors. However, it is recognized that malignant neoplasms are found associated more often with carcinoid than with other tumors. Thus Pearson and Fitzgerald[8] report an instance of 31 per cent of other malignant disease in the 29 non-appendiceal carcinoid tumors.

Malignancy. Though none of the duodenal carcinoids so far encountered have been malignant, they have been reported so rarely in this site that their malignant potentialities cannot be established accurately. However, these tumors in other portions of the intestinal tract have been evaluated amply. Ritchie and Stafford[10] reviewed 332 argentaffin tumors and found evidence of metastasis in 37.9 per cent. These authors are careful to note, however, that metastasis is used in a widely varying meaning, the term being used by some even if only the muscle coat and mesentery are involved. Cooke[4] in 1931 found reports of 104 carcinoids of the small intestine, including 2 in the duodenum, and added a group of 11, 3 of which were malignant and 8 of which were benign. Of the 115 tumors, 24 (all primary in the ileum) are recorded as malignant but the majority of these that were so designated showed only local direct extension and were without distant metastases; thus 3 extended to the serosa only, 10 to regional lymph nodes, and only 11 showed distant metastases. Porter and Whelan,[9] reporting 84 cases, found 9 in the small intestine, and 1 in the duodenum. Two of the ileal neoplasms showed local extension and 1 metastasized distantly. In a recent report of Pearson and Fitzgerald,[8] 23 small intestinal carcinoids are recorded, of which 20 occurred in the ileum, 2 in the jejunum and 1 in the duodenum. Seven of the ileal tumors showed local extension to serosa, mesenteric nodes or mesentery or omentum, and 3 showed distant metastasis. Ritchie and Stafford,[10] in their own series, record 9 carcinoids of the small intestine, 8 of which were in the ileum, and 1 in the duodenum. Two of the ileal tumors showed distant metastases and 1 local extension. Thus, as adequately documented, these tumors occasionally produce distant metastases when arising in the ileum but more often are malignant only in the sense of local infiltration. Though there are instances of relatively rapid growth in the small intestine, they usually are slowly growing neoplasms. Metastasis was not noted in the reports reviewed. However, though generally slowly growing, it seems unlikely that they are to be regarded as totally benign in the duodenum, considering their character in other portions of the small intestine. The tumors recorded in

this report showed only local infiltration of mucosa and submucosa, and in one instance adjoining muscularis. Time and circumstances have not permitted sufficient follow-up for clinical evaluation of these 3 cases and too few carcinoids of the duodenum are on record for accurate estimation of the metastatic potentiality.

Prognosis. Two of the patients have had progress roentgenographic examination. One patient, Case III, was seen eleven months after excision of her carcinoid and there was no roentgen evidence of recurrence. One patient, Case I, was seen twenty-eight months after excision and there was no recurrence, subsequently the duodenum was examined during an exploratory operation and was reported as normal. Because of the usually low grade of malignancy of carcinoid tumors, it seems probable that local excision of the tumor should afford an excellent prognosis.

Treatment. Since it does not seem possible to differentiate the benign duodenal tumors from carcinoid which may have malignant potentialities the procedure of choice is local excision of all such tumors for histopathologic evaluation. After removal of the neoplasm, it is extremely important that they be recognized for their true worth, rather than as carcinoma.

Roentgen Diagnosis. There appears to be no way to establish the diagnosis of a duodenal carcinoid roentgenologically. In the 3 patients reported here, the only significant roentgen criterion was a solitary rounded defect in the duodenal bulb. This type of defect cannot be considered characteristic of carcinoid, however, as the reports of Carman,[3] Camp,[2] and Golden[5] indicate that a variety of benign duodenal tumors produce a rounded or vacuolated defect. Waters[11] maintained that a vacuolated filling defect in the duodenum indicated an adenoma and that a multilocular defect was diagnostic evidence of a papilloma. Overgaard,[7] in a recent discussion of polyps of the stomach and duodenum, has regarded sharply circumscribed or lobulated filling defects in the duodenum or stomach as characteristic of polyps. None of the carcinoids in the present reports have shown roentgen evidence of polylobulation, but neither were roentgen criteria evident whereby the sharply demarcated filling defects could be differentiated from those of an adenoma, myoma, papilloma, or pancreatic rest. None of these tumors could be massaged through the pylorus and into the stomach, nor could a stalk or pedicle be identified.

SUMMARY

Three cases of carcinoid of the duodenum have been presented. All showed a rounded filling defect in the duodenal bulb indistinguishable from benign tumors. Pathologically they were locally invasive, involving submucosa (in one instance immediately adjoining muscularis), and presented the histopathologic appearance typical of carcinoid. All were locally excised by transduodenal operation. Roentgenologic and pathologic features are discussed.

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SUBPERIOSTEAL RESORPTION OF BONE

A ROENTGENOLOGIC MANIFESTATION OF PRIMARY HYPERPARATHYROIDISM AND RENAL OSTEODYSTROPHY*

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SUBPERIOSTEAL resorption of bone was first described by Camp and Ochsner[3] in 1931 in a paper on the roentgenologic manifestations of the osseous changes in hyperparathyroidism. Since then many investigators have observed subperiosteal resorption of bone in primary hyperparathyroidism and also in renal osteodystrophy. The great significance of this form of osseous change, however, has not been generally recognized, and its value in diagnosis has not been properly stressed.

The purpose of this investigation has been to determine the frequency of occurrence of subperiosteal resorption of bone in primary hyperparathyroidism and in renal osteodystrophy. Various forms of osteomalacia and osteoporosis also were studied to determine whether subperiosteal resorption of bone occurred in those conditions.

DESCRIPTION

In the roentgenogram, subperiosteal resorption of bone is seen most frequently along the margins of the phalanges of the hands, especially the middle phalanges (Fig. 1). This resorption does not consist of a mere decalcification of the cortex but rather gives a peculiar lace-like appearance to the bone beneath the periosteum. Sometimes the external surface of the cortex has a ragged spicule-like appearance. Some investigators have used the term "palisade-like periosteal new bone formation" to describe this appearance. This term is hardly correct, since the changes seen are not the result of formation of new bone but rather the result of resorption of bone. In extreme cases the cortex may be completely absorbed. When the distal phalanges are affected, the tufts tend to be absorbed. At times the subperiosteal resorption of bone occurs around the joint, in which case the appearance is somewhat suggestive of rheumatoid arthritis, but none of the patients in my series who had this type of change had any clinical evidence of arthritis (Fig. 2*a*). Although the phalanges of the hands are affected most frequently, it is unusual to see subperiosteal resorption of bone in the phalanges of the feet.

The next most frequent site of subperiosteal resorption of bone is along the medial aspect of the upper third of the tibia. On

FIG. 1. Primary hyperparathyroidism. There is marked subperiosteal resorption of bone in the phalanges and the tufts are partially absorbed.

* Presented at the Fifty-first Annual Meeting, American Roentgen Ray Society, St. Louis, Mo., Sept. 26–29, 1950.

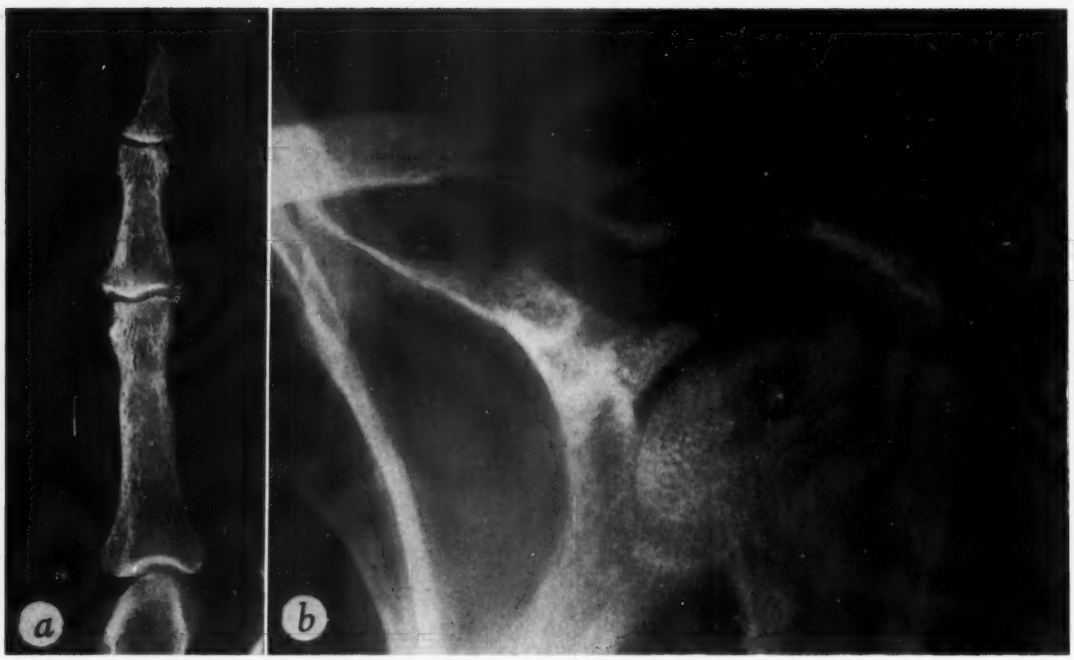

Fig. 2. Primary hyperparathyroidism. *a*. The subperiosteal resorption of bone is most conspicuous in the region of the interphalangeal joints, resembling that in rheumatoid arthritis; the tuft is partially absorbed. *b*. On the inferior aspect of the distal third of the clavicle subperiosteal resorption of bone can be seen.

Fig. 3. Primary hyperparathyroidism. There is subperiosteal resorption of bone along the distal end of the shaft of the ulna.

occasion the inferior aspect of the distal third of the clavicle (Fig. 2*b*) and the margins of the distal end of the ulna (Fig. 3) are involved. Since subperiosteal resorption of bone occurs with much greater frequency in the phalanges, it is there that one should look for this type of osseous change. In many instances the resorption of bone is conspicuous, but in other cases it is necessary that roentgenograms of the finest quality be obtained in order to demonstrate this change. After the state of hyperparathyroidism has been corrected by operation, subperiosteal bone is rapidly regenerated and the cortex appears normal. There is never any permanent loss of the cortex. The tufts are completely re-formed (Fig. 4).

The loss of the lamina dura which is seen in dental roentgenograms is another manifestation of subperiosteal resorption of bone. This has been emphasized many times in the literature and will not be discussed in detail in this paper. The periodontal membrane is a specialized form of periosteum. The lamina dura is actually the cortical portion of bone around the teeth. Without going into a consideration of the

value of the loss of lamina dura in the diagnosis of hyperparathyroidism and renal osteodystrophy, it still should be mentioned that the loss of the lamina dura has been reported as occurring in other conditions besides hyperparathyroidism and renal osteodystrophy. There is no lamina dura in edentulous patients, and, therefore, in many elderely persons the loss of the lamina dura cannot be depended on as a diagnostic criterion.

Fig. 4. Primary hyperparathyroidism. *a.* Before operation, showing extensive subperiosteal resorption of bone. *b.* Three years after a parathyroid adenoma was removed. The subperiosteal bone has been restored completely.

MATERIAL STUDIED AND RESULTS

Hyperparathyroidism. The clinical and roentgenologic aspects in 76 cases of primary hyperparathyroidism in which parathyroid adenomas or primary hyperplasia of the parathyroid glands was demonstrated at operation were studied (Table 1). Of this group, 38 patients (50 per cent) gave no roentgenologic evidence of disease of the bone. All but 5 of these had urinary calculi. The average of the alkaline phosphatase of the serum in 33 cases in which it was determined by the Bodansky method was 2.9 Bodansky units. The highest determination in any case in this group was 6.0 Bodansky units. Three patients had the concentration of alkaline phosphatase determined by the King-Armstrong method, and the average was 4.8 units. The very low alkaline phosphatase in all the cases of this group gives evidence that there was no disease of the bone and that none should have been expected to have been seen roentgenologically.

In 11 cases (14 per cent) of primary hyperparathyroidism, slight or moderate decalcification of the skeleton was seen roentgenologically without any evidence of subperiosteal resorption of bone. In none of

Table I

HYPERPARATHYROIDISM

Roentgenologic Findings	Cases		Alkaline Phosphatase					
			Bodansky units			King-Armstrong units		
	No.	Per cent	No. examined	Average	Highest	No. examined	Average	Highest
No subperiosteal resorption								
No abnormality of bone	38	50	33	2.9	6.0	3	4.8	6.2
Slight or moderate decalcification	11	14	10	3.4	4.4			
Cysts of bone	2	3	2	3.8	5.3			
Subperiosteal resorption of bone	25	33	23	16.4	43.1			
Total	76	100						

these cases was there sufficient abnormality of the bone to justify the roentgenologic diagnosis of hyperparathyroidism and in none were cysts of the bone present. The level of the alkaline phosphatase of the serum in 10 cases in this group averaged 3.4 Bodansky units. The highest determination of alkaline phosphatase in this group was 4.4 Bodansky units. It is obvious, therefore, that there could not have been much bone disease, and it is questionable whether the decalcification that was seen was the result of hyperparathyroidism or whether it was due to some type of osteoporosis.

In 2 cases (3 per cent) of primary hyperparathyroidism, cysts of the bone were seen without any evidence of subperiosteal resorption of bone. One of these paitents had a duodenal ulcer and had been on a milk diet. The increase of calcium that had been taken in this way seemed to have healed the skeletal disease, since the cysts that were present showed rather dense calcification around the margins. This undoubtedly explains the fact that no subperiosteal resorption of bone was seen. The absence of subperiosteal resorption of bone in the other case could not be explained, but since the concentration of alkaline phosphatase in this case was only 5.3 Bodansky units, it seems that for some reason the disease of the bone had become inactive.

In 25 cases (33 per cent) of primary hyperparathyroidism subperiosteal resorption of bone was evident. In 23 cases of this group the level of the alkaline phosphatase averaged 16.4 Bodansky units. The highest value of alkaline phosphatase was 43.1 Bodansky units and the lowest was 6.7 Bodansky units. Therefore, it is obvious that in all of these cases there was definite evidence of disease of the bone. Of these 25 patients only 9 had urinary calculi.

It seems significant that all of the patients who had hyperparathyroidism and an elevated value for alkaline phosphatase showed subperiosteal resorption of bone and, conversely, none of those who had a normal alkaline phosphatase showed subperiosteal resorption of bone. Therefore,

TABLE II

RENAL INSUFFICIENCY (GLOMERULAR)

Roentgenologic Findings	Cases		Average Values					
	No.	Per cent	Urea, mg. per 100 cc.	CO_2, vol. per cent	Creatinine, mg. per 100 cc.	Calcium, mg. per 100 cc.	Phosphorus, mg. per 100 cc.	Alkaline phosphatase, Bodansky units
Decalcification (no rickets or resorption)	7	20	105 (7)*	—	14.4 (1)	9.9 (5)	4.9 (5)	12.6 (1)
Rachitic changes (no subperiosteal resorption)	2	6	96 (2)	12.6 (1)	—	7.4 (2)	4.7 (2)	—
Subperiosteal resorption of bone	26	74	234 (26)	20.8 (20)	8.1 (20)	8.4 (25)	6.5 (24)	22.7† (11)
Total	35	100						

* The numbers in parentheses indicate the number of patients examined.
† Highest value was 74.6 Bodansky units.

It seems significant that all of the patients who had hyperparathyroidism and an elevated value for alkaline phosphatase showed subperiosteal resorption of bone and, conversely, none of those who had a normal alkaline phosphatase showed subperiosteal resorption of bone. Therefore,

if there is no elevation of the alkaline phosphatase, one should not expect to see much skeletal evidence of that disease, since the level of the serum alkaline phosphatase does seem to be a most accurate indication of skeletal disease in hyperparathyroidism.

The Renal Insufficiency. Thirty-five cases were studied in which the diagnosis of renal rickets, renal dwarfism, renal infantilism or renal osteodystrophy had been made (Table II). Seven patients (20 per cent) had renal insufficiency with generalized decalcification but without rickets or evidence of subperiosteal resorption of bone. Six of these were children and showed dwarfism or infantilism. One was an adult who had a pathologic fracture of the femur. The renal disease in this group was not especially severe except for that of the adult patient. The concentration of urea averaged 105 mg. per 100 cc. of blood in these 7 cases. The creatinine was determined only for the adult patient, and in this instance it was found to be greatly elevated, being 14.4 mg. per 100 cc. of blood. In all cases there was a low fixed specific gravity of the urine. The level of the serum calcium was normal, averaging 9.9 mg. per 100 cc. in the 5 cases in which it was studied. The level of the serum phosphorus was normal, in the cases in which it was studied.

Two patients (6 per cent) were studied who had renal insufficiency and showed rachitic changes but without subperiosteal resorption of bone. The values of urea in these 2 cases were 118 and 74 mg. per 100 cc., with a low fixed specific gravity of the urine in the first case. The level of the serum calcium in this group was low, being 8.6 and 6.3 mg. per 100 cc. The level of the serum phosphorus was 5.6 and 3.9 mg. per 100 cc., and this was within normal limits for patients of their age. The relatively mild degree of decalcification of the bone in these cases was probably due to the acidosis which was present with osteomalacia resulting, but there was not sufficient urinary insufficiency and chemical imbalance of the blood to cause the more severe manifestations of renal osteodystrophy.

There were 26 patients (74 per cent) who had renal insufficiency who showed subperiosteal resorption of bone. Seven of these patients were more than twenty years of age. All had severe renal insufficiency. All but 2 had definite acidosis. This was shown by a lowered carbon dioxide combining power which averaged 20.8 volumes per cent for the 20 patients who were so studied. In most instances there was definite elevation of the level of the serum phosphorus which averaged 6.5 mg. per 100 cc. in the 24 cases in which it was studied. This is abnormally high for persons of the ages of the patients in this series. However, 5 patients in this group gave no evidence of renal retention of phosphorus. The level of the serum calcium in 25 cases of this

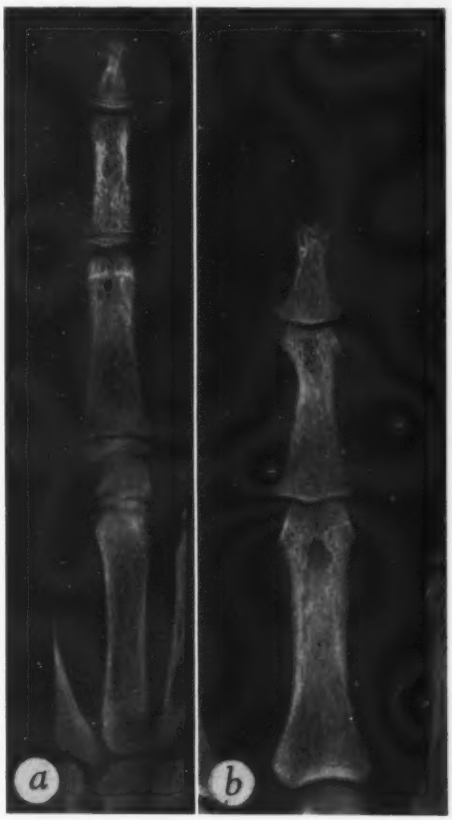

FIG. 5. Renal osteodystrophy; subperiosteal resorption of bone in the phalanges identical with that seen in primary hyperparathyroidism. *a.* Patient, aged fifteen. *b.* Patient, aged twenty-nine. Most conspicuous resorption along one side of the middle phalanx.

Fig. 6. Renal osteodystrophy; patient, aged twelve. Subperiosteal resorption of bone can be seen on the medial aspect of the upper part of the tibia. An identical change occurs in primary hyperparathyroidism.

group averaged 8.4 mg. per 100 cc. In 11 cases the average of the alkaline phosphatase was 22.7 Bodansky units, the highest being 74.6 Bodansky units and the lowest 6.6 Bodansky units. In 1 case the alkaline phosphatase was determined by the King-Armstrong method and it was 38.9 units, which is high.

The subperiosteal resorption of bone

Fig. 7. Renal osteodystrophy; patient, aged twenty-three. Absorption of bone at the margins of the sacroiliac joints resembles the changes seen in early rheumatoid spondylitis.

that was seen in these 26 cases of renal osteodystrophy was identical with the changes that occurred in the cases of primary hyperparathyroidism (Fig. 5, *a* and *b*, and 6). A peculiar manifestation of resorption of bone was seen along the margins of the sacroiliac joints in the adult patients.

Fig. 8. Osteomalacia. Although there is marked decalcification of the bone no subperiosteal resorption of bone has occurred.

The resorption of bone here caused the sacroiliac joints to become indistinct, and the appearance was suggestive of rheumatoid spondylitis (Fig. 7). In fact, that diagnosis has been suggested in 2 cases of this group.

Osteomalacia. Fifteen cases of osteomalacia were studied. Included were 3 cases of osteomalacia of unknown origin (Fig. 8), 4 of sprue, 1 case of dietary deficiency, 1 in which there was excessive urinary excretion of calcium and phosphorus without evi-

dence of hyperparathyroidism, 2 cases of diabetes with chronic acidosis, 2 of tubular insufficiency without glomerular insufficiency (Fig. 9) and 2 of Fanconi's disease (Fig. 10). In none of these was there any evidence of subperiosteal resorption of bone. At times the cortex of the bone showed decalcification, but there was never any suggestion of the lace-like appearance of the subperiosteal bone which is so characteristic of primary hyperparathyroidism and renal osteodystrophy.

Osteoporosis. Subperiosteal resorption of bone does not occur in osteoporosis; osteoporosis may be defined as a condition in which there is a deficiency in the organic matrix of bone. Many cases of postmenopausal and senile osteoporosis were studied and there was never any suggestion of subperiosteal resorption of bone. In Cushing's disease, which causes osteoporosis, the abnormality of the bone may be great, but in the 3 cases recently studied there was no evidence of subperiosteal resorption of bone and the bone in general did not resemble that in hyperparathyroidism (Fig. 11). Although osteoporosis occurs occasionally in hyperthyroidism, subperiosteal resorption of bone is not seen in that condition.

Fig. 9. Tubular insufficiency without glomerular insufficiency. There are rachitic changes especially in the wrist but no subperiosteal resorption of bone can be seen.

Fig. 10. Fanconi's disease; patient aged one year. There is decalcification of the bone with rachitic changes at the distal ends of the radius and ulna. In the distal third of the radius is a pathologic fracture. No subperiosteal resorption of bone can be seen.

Hypervitaminosis D. Since in toxic doses vitamin D seems to have an action somewhat similar to that of parathyroid hor-

Fig. 11. Cushing's disease. There was generalized osteoporosis of marked degree. Many ribs showed pathologic fractures. No subperiosteal resorption of bone occurred.

mone, it was thought that subperiosteal resorption of bone might occur in cases of hypervitaminosis D. In 3 cases of well-established hypervitaminosis D in which decalcification of bone and periarticular calcinosis had occurred, no subperiosteal resorption of bone could be seen (Fig. 12) and no one has reported such a change in the literature.

COMMENT

There seems ample evidence to support the thesis that subperiosteal resorption of bone occurs only in primary hyperparathyroidism and in renal osteodystrophy. There is also evidence, not only roentgenologic but pathologic, to support the concept that in renal osteodystrophy with subperiosteal resorption of bone a state of secondary hyperparathyroidism is present. The mechanism by which the parathyroid glands are stimulated in this way in cases of renal osteodystrophy has not been well established. It has been stated that in renal osteodystrophy the retention of phosphorus causes a compensatory tendency toward lowering of the serum calcium, and this in turn causes secondary hyperparathyroidism with the withdrawal of calcium and phosphorus from bone.[1,2] This seems like a logical explanation, except that in cases of osteomalacia the level of the serum calcium often is extremely low and in fact much lower than ever encountered in renal osteodystrophy, and yet there is never any

Fig. 12. Gout with hypervitaminosis D. Calcium has been deposited in a large gouty tophus at the proximal interphalangeal joint of the middle finger as the result of vitamin D intoxication. There is no subperiosteal resorption of bone.

roentgenologic evidence of secondary hyperparathyroidism in this group and osteitis fibrosa is never seen pathologically. It seems that if the lowering of the serum calcium were to cause secondary hyperparathyroidism, it would certainly take place in cases of sprue in which the levels of serum calcium are often as low as 4 or 5 mg. per 100 cc.

It has been stated that in patients with renal osteodystrophy the phosphorus that is retained in the serum is excreted into the gastrointestinal tract and binds calcium so that it cannot be absorbed.[5] This may be the case, since there was evidence of lowered concentration of serum calcium in all of the cases of this condition which I studied, and this could be explained on the basis of lack of absorption of calcium, yet that would cause only the osteomalacia and the appearance would not be one of hyperparathyroidism. There are those who contend that the bone changes in renal osteodystrophy are the result of chronic acidosis.[2] This would cause calcium to be lost as a fixed base, and again this would cause osteomalacia and the bones would then resemble those seen in cases of chronic acidosis associated with diabetes or in renal tubular insufficiency without glomerular insufficiency, and that is not the case.

There is some evidence to suggest that perhaps the secondary hyperparathyroidism that is present in renal osteodystrophy may be a direct effect of the elevation of serum phosphorus on the parathyroid glands. However, in 5 of our cases of renal osteodystrophy with subperiosteal resorption of bone, levels of serum phosphorus were normal. Since in some cases of renal osteodystrophy the serum phosphorus is not appreciably elevated, although the bone is markedly abnormal, it is rather difficult to explain the secondary hyperparathyroidism on the basis of renal retention of phosphorus.

The mechanism whereby secondary hyperparathyroidism occurs in renal osteodystrophy is, therefore, still obscure. Ginzler and Jaffe[4] have shown by pathologic studies that in cases of relatively mild renal insufficiency the abnormality of the bone may not be great and can be explained on the basis of chronic acidosis. They stated, also, that in cases of severe renal osteodystrophy the changes in the bone can be acounted for only by secondary hyperparathyroidism. The roentgenologic and pathologic evidence indicating the identical nature of the lesions of the bones in renal osteodystrophy and primary hyperparathyroidism cannot be ignored. In osteomalacia, rickets, carcinomatosis, multiple myeloma and pregnancy, hypertrophy of the parathyroid glands may occur. Since none of these conditions show any roentgenologic evidence of secondary hyperparathyroidism, it seems that the hypertrophy of the parathyroid glands that occurs in these conditions is a well-regulated compensatory mechanism. The type of parathyroid response that occurs in renal insufficiency suggests that it may be a truly toxic one and not a purely compensatory mechanism.

Subperiosteal resorption of bone is a great aid in the diagnosis of primary hyperparathyroidism and renal osteodystrophy. It does not occur in other conditions and, therefore, it is pathognomonic of those two diseases. In questionable cases of hyperparathyroidism or renal osteodystrophy roentgenograms of the hands should always be taken.

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DISCUSSION

Dr. John F. Holt, Ann Arbor, Michigan. Dr. Pugh is to be commended for his excellent presentation which once again points up the advisability of obtaining films of the hands and feet as a part of any roentgenologic skeletal survey, especially when one is dealing with metabolic bone disease. All too many of us are inclined to think of a request for "films of the long bones" in literal terms, thereby omitting from our survey some 76 tubular bones, any of which might contain the important diagnostic information which we seek.

I would like to call your attention to Dr. Pugh's correct usage of the terms osteoporosis, osteomalacia and osteitis fibrosa, terms which we as radiologists are apt to use in a very loose manner in describing localized or generalized demineralization of bone when the etiology of the condition in question is not clearly evident. *Osteoporosis* is, by modern definition, a disorder of tissue metabolism in which the osteoblasts lay down too little bone matrix. *Osteomalacia*, on the other hand, is a disorder of calcium-phosphorus metabolism in which calcium salts are not deposited in the newly formed bone matrix. *Osteitis fibrosa cystica* (hyperparathyroidism) is a disorder of both the bone matrix and calcium-phosphorus metabolism characterized by tremendously increased bone resorption. Thus, unless we have diagnostic roentgenologic findings in a situation where there is diminished bone density, we should be cautious in the use of our terminology. Incidentally, if these metabolic diseases of bone are as confusing to you as they are to me, I suggest that you keep handy Albright and Reifenstein's book "The Parathyroid Glands and Metabolic Bone Disease." This little volume is one of the classics of modern medical writing.

Just a word about the signs which Dr. Pugh has described in the differential diagnosis of polyostotic fibrous dysplasia and hyperparathyroidism. Whereas one might think that there should be no excuse for confusing these two diseases, it appears that von Recklinghausen did so in his original description of osteitis fibrosa cystica, and furthermore a sizable number of patients with polyostotic fibrous dysplasia have had ill-fated exploratory operations for parathyroid adenomas. Although the obvious roentgenologic differences can be detected in any involved portion of the skeletal system, nowhere are these differences more striking than in the bones of the hands, providing of course, these structures are affected.

I am especially grateful to Dr. Pugh for showing me typical subperiosteal bone resorption in patients with so-called renal rickets. Previously, it has always been difficult for me to accept Dr. Albright's seemingly incontrovertible histopathological evidence that the bone changes in this disease were due to secondary hyperparathyroidism, merely because the cases I have seen have been so typical of rickets with none of the roentgenologic signs of hyperparathyroidism.

Finally, without detracting in the slightest from Dr. Pugh's spendid presentation today, may I express the hope that, with the vast storehouse of material on hyperparathyroidism at his disposal, he will see fit to supply the radiologic literature with a much-needed comprehensive article on the subject, covering all the many roentgenologic features of the disease.

Vol. 66, No. 4

THE ROENTGEN APPEARANCE OF EARLY PAGET'S DISEASE*

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PAGET'S disease or osteitis deformans is characterized by the simultaneous absorption of bone and the formation of new bone of an abnormal character. The roentgenographic appearance of these osseous alterations is well known and consists of thickening of the bony cortex and coarsened trabeculation of the cancellous portion. If these processes of bone absorption and new bone formation are not simultaneous, a totally different roentgenographic picture may result that is not so readily recognized as Paget's disease. This difficulty is well demonstrated in Case 1, reported below, in which the initial appearance was an expansile osteolytic lesion of the anterior cortex of the tibia but the thickened cortex and coarse trabeculations characteristic of osteitis deformans developed subsequently during an observation period of thirteen years. When first observed, neither the roentgenograms nor the microscopic anatomy suggested classical Paget's disease. A second patient presented similar histopathologic and roentgenographic findings, but has been followed for a shorter period of time. Both cases are thought to represent an early phase in the pathogenesis of this disease, manifested chiefly by bone resorption. Since the roentgen appearance seems to be quite characteristic although different from that of the well developed disease, a description was felt to be warranted, and may be of value in the study of the pathogenesis of Paget's disease.

Case 1. A.W. (N.H. Hospital No. 362041). This patient, a white male of Italian extraction, had been a frequent visitor to the urology clinic since the age of nineteen because of prostatitis and urethritis, although no evidence of gonorrhea or syphilis had ever been found. On one of his routine vists to the clinic at the age of 27, he complained of a mild, dull aching pain in the right lower leg of two months' duration. Physical examination revealed a firm swelling on the anterior surface of the tibia without redness or heat. Roentgenograms taken at this time revealed a radiolucent expansion of the anterior cortex of the mid-shaft of the tibia and was interpreted as being compatible with the diagnosis of osteoperiostitis. The following month, in August, 1935, he was admitted to the hospital for biopsy and a small fragment of cortex measuring $\frac{1}{4}$ by $\frac{1}{4}$ by $\frac{3}{16}$ in. was removed. Very little bleeding occurred and the bone seemed to be denser than normal. The pathologist's report at that time was as follows: "The specimen measures 1 by 0.6 by 0.6 cm. and is composed chiefly of bony tissue. The slide shows a pink staining matrix with here and there a purple tinge. Within the matrix are many small lacunae containing basophilic nuclei. There are many large irregularly shaped spaces which contain a light-staining, purple-pink tissue with basophilic nuclei (osteoclasts and osteoblasts). There are many such spaces which contain multinucleated giant cells. The tissue has the appearance of increased activity (bone production and bone destruction). There is no periosteum on these sections."

He was discharged from the hospital two days later and was seen at a follow-up visit twelve days after the biopsy, at which time the wound seemed to be well healed so that he was advised to discard the crutches which he had been using. The following evening, while walking down the street, he suddenly heard a distinct snapping sound in the right leg and found that he was unable to stand. Roentgenograms showed an incomplete transverse fracture of the middle third of the tibia. The leg was immobilized and the fracture healed without difficulty.

In February, 1936, the films of the extremities were reviewed by Dr. H. M. Wilson, who thought that the tibial lesion was highly suggestive of the type of bone lesion associated with osteoporosis circumscripta of the skull as reported by Kasabach and Dyke.[13] Skull films taken at that time were negative.

* From the Department of Radiology, Yale University School of Medicine, New Haven, Connecticut, and Department of Radiology, Washington University School of Medicine, Edward Mallinckrodt Institute of Radiology, St. Louis, Missouri.

In June, 1936, the patient was referred to the medical clinic for metabolic investigation because of recurrent renal calculi and the first blood chemical analyses were done with the following results: serum calcium 10.57 mg. per cent; serum phosphorus 3.81 mg. per cent; total protein 6.96 gm. per 100 cc. with an albumin fraction of 4.96 gm. and globulin of 2.0 gm.; non-protein nitrogen 32 mg. per cent. It was felt that there was no evidence of hyperparathyroidism.

Fig. 1. Lateral view of the right tibia of Case 1 showing a rarefied expansion of the anterior cortex with sharply limited borders. Note the characteristic V-shaped upper and lower limits of the lesion.

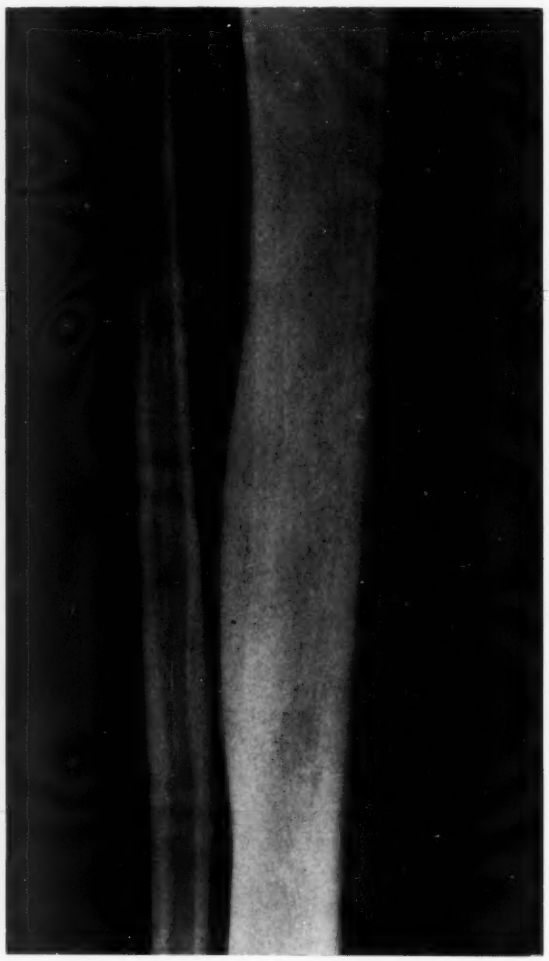

Fig. 2. Frontal view of tibia shown in Figure 1. Note the expansion of cortex which presents on the lateral aspect of the tibia and suggests periosteal new bone formation in this projection.

During the subsequent ten years he was seen at frequent intervals in the urology clinic for his kidney stones but did not complain of his leg again until February, 1947, when he was seen in the orthopedic clinic because of swelling of the right tibia and pain which occurred only while walking barefoot. Roentgenograms disclosed a thickened cortex, coarse trabeculations and anterior bowing of the tibia, characteristic of Paget's disease. The alkaline phosphatase level was found to be 13.3 King-Armstrong units. Numerous serological tests for syphilis were negative.

During the subsequent two years, numerous studies were done because of recurrent renal calculi in order to detect any abnormalities in his calcium metabolism, but none were found. He was last seen in April, 1949, when examination of the leg revealed no tenderness but the skin over the right leg was distinctly warmer than on the left. The alkaline phosphatase at

this time was 10.1 King-Armstrong units. Roentgen examination of his entire skeleton failed to reveal any other bony abnormalities and there was no significant change in the appearance of this right tibia as compared to the roentgenograms of February, 1947. Since the patient had no complaints referable to his leg, he would not agree to another bone biopsy.

Fig. 3. Photomicrograph of the biopsy taken from the right tibia of Case 1 showing vascular connective tissue lying in the lacunae and an increased number of cement lines.

The slides and films were sent to Dr. Fuller Albright, who thought that the biopsy showed increased bone formation and bone resorption with increased fibrosis consistent with Paget's disease, although the mosaic structure which is pathognomonic of Paget's disease was present to only a limited degree. After looking over the roentgenograms, Dr. Albright thought that it was unquestionably Paget's disease. The films were also presented to Dr. J. R. Brailsford who agreed with the diagnosis.

Case II. R.D.B. (Barnes Hospital No. 166715). (Used with the permission of Dr. L. T. Furlow). This twenty-four year old farmer was admitted to Barnes Hospital because of a severe headache coming on one week after an automobile accident. As an incidental finding a swelling was noted over the anterior right tibia. Patient stated that he had noted this for one year but during the past six months there had been some increase in size and moderate pain when running or during prolonged standing. Six weeks earlier he noted that his leg became red and swollen after playing football. Because of this he consulted his physician who took roentgenograms and recommended a biopsy.

Roentgenograms of the tibia revealed fusiform expansion of the anterior cortex, with obliteration of trabeculation and anterior bowing.

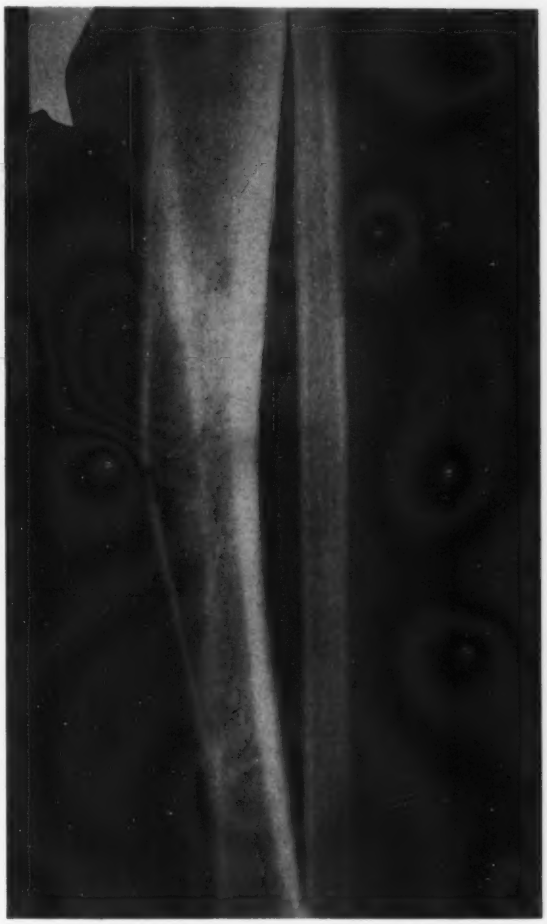

Fig. 4. Case 1. Roentgenogram of right tibia taken six weeks after Figures 1 and 2 showing the transverse comminuted fracture occurring in the mid-portion of the expanded tibial cortex.

The upper and lower margins exhibited a V-shaped demarcation from the adjacent bone which appeared normal except for a few coarsened trabeculae, suggestive of early pagetoid changes. A rectangular defect, marking the site of the biopsy was present in the mid portion of the fusiform enlargement. The posterior cortex was normal, as well as the rest of the skeleton.

The sections of the biopsy specimen showed adult bone without evidence of abnormalities.

Blood counts, non-protein nitrogen determinations and serological studies were all negative. Calcium, phosphorus, and alkaline phosphatase determinations were not done.

Re-examination six months later revealed an increased thickening of the trabeculations in the adjacent bone suggesting a beginning transition into classical Paget's disease.

Fig. 5. Case 1. One month after the fracture with extension of the osteolytic process and beginning thickening of the trabeculae suggesting early pagetoid changes.

Fig. 6. Case 1. One year following the pathologic fracture with sclerosis of the previously osteolytic lesion.

Dr. Sherwood Moore measured the skin temperature over the anterior portion of each leg and noted a temperature of 33° C. over the normal leg, and 35.8° C. over the diseased leg.

CLINICAL ASPECTS

Because of the recurrent bilateral renal calculi in Case 1, hyperparathyroidism was suspected but no confirmatory evidence could be found. Serum calcium and serum phosphorus concentrations were within the limits of normal on numerous occasions. This is in accord with the findings of Gutman, Tyson and Gutman[11] that the serum calcium and phosphorus levels are rarely disturbed in Paget's disease. The association of urinary calculi with Paget's disease has been noted by others. Goldstein and Abeshouse[8] reported 6 cases of Paget's disease with urinary calculi. Twenty-two of the 367 cases reported by Dickson *et al.*[6] and 4.9 per cent of 82 cases reported by Newman[17] had urinary calculi although no one has offered any satisfactory explanation for this coincidence.

The normal value of the serum alkaline phosphatase is probably best explained by the predominance of the osteolytic process since elevation of the phosphatase in this disease is an index of osteoblastic activity.[11] Dickson *et al.*[6] point out that the serum phosphatase is of little diagnostic value in early localized forms of Paget's disease since the elevation is slight or absent. This could also be explained on the presence of only a relatively small area of bone involvement since a rough proportionality exists between the extent of disease and the phosphatase activity.[11] In Groh's[9] series of 9 cases of mono-osteitic Paget's disease the highest value was 14.6 Bodansky units.

It is a little unusual for Paget's disease to occur in a patient as young as the ones reported above, since the average age incidence in most series is in the sixth decade. This disease may be present for years without producing symptoms and be discovered in the course of a routine examination.[6] However, one of Paget's original patients was only twenty-eight at the time of onset of his disease and both Dickson[6] and Brailsford[4] described patients who were in their late twenties at the time of diagnosis. More recently an authenticated case occurring in an eighteen year old male has been reported.[23]

The occurrence of a pathological fracture is not unusual for it is the most frequent complication of Paget's disease. Seventy-two fractures occurred in Dickson's series of 367 patients, in addition to seven incomplete fissure fractures. According to Ghormley *et al.*[7] the incidence of pathological fractures in Paget's disease is 8 per cent. Fissure fractures were first demonstrated roentgenologically by Salinger who interpreted them as the Looser zones that had been described in osteomalacia and late rickets. Schmorl, however, concluded that they were true traumatic fractures.

Fig. 7. Case 1. Appearance of the same tibia thirteen years later which now has the roentgen characteristics of classical Paget's disease.

MICROSCOPIC PATHOLOGY

The histopathological appearance of the biopsy specimens in these cases is not the classical picture of fragments of lamellar bone separated by numerous cement lines with absence of the Haversian canals as described by Schmorl.[20] This typical architecture is seen only in completely transformed Paget's bone. As Schmorl pointed out, if absorption is very rapid the mosaic arrangement does not occur and the original bone may be replaced by connective tissue. According to him, the earliest changes consist of the presence of numerous osteoclasts lying in Howship's lacunae within the vascular canals. The latter progressively enlarge and additional osteoclasts appear and the canals become filled with connective tissue. The specimen from Case 1 was interpreted as containing increased osteoclasts and an increased

amount of connective tissue between the trabeculae and thus seemed to resemble Schmorl's description. In the second case only normal bone was found on the biopsy but the specimen may not have been representative.

Fig. 8. Roentgenogram of the right tibia of Case II, showing an expansile, osteolytic lesion of the anterior cortex very similar to the tibia in Figure 1. Central defect represents the biopsy site.

Fig. 9. Case II six months later with beginning cortical sclerosis and coarsening of the trabeculae.

ROENTGEN APPEARANCE

The characteristic roentgen findings in early Paget's disease were emphasized by Brailsford[3,4] who reported the occurrence of Paget's disease in a twenty-seven year old male with a tender swelling over the tibial tubercle. The roentgenogram was described as showing, "a lanceolate area of subcortical decalcification with obliteration of cancellous detail within" and production of an ovoid cyst-like structure. He stressed the sharp V-shaped line of demarcation which delimits the disorder above and below. The diagnosis of Paget's disease in Brailsford's case was based on the presence of a few coarsened trabeculae in the femur and by the subsequent development of the typical changes. Case VII of Kasabach and Dyke[13] had a fusiform enlargement of the midshaft of the left tibia whose cortex was described as appearing thinner than usual along the anterior margin. Similar lesions have been mentioned by Meyer-Borstel[15] and Eisler. Albright has a patient with almost identical roentgenograms.[2]

The differential diagnosis of the thickened, hyperplastic lesion as exemplified by roentgenograms in the later stages is not difficult, and probably only syphilis and osteoblastic carcinoma are worthy of con-

sideration and are easily excluded. The cysts that are seen in advanced Paget's disease bear no similarity to this early cyst-like lesion either roentgenologically or histopathologically since they occur in the cancellous portions of tubular bones that are markedly thickened and hyperplastic. Pathologically they have been described by Jaffe[12] as fat-filled marrow spaces delineated by thickened sclerotic trabeculae that only simulate cysts on the roentgenogram. The early rarefied lesions could perhaps be confused with other processes productive of cystic lesions. It is felt, however, that the fusiform, radiolucent, expansile process limited to the cortex with a sharp V-shaped demarcation at the upper and lower limits of the lesion is almost as pathognomonic of early osteitis deformans as the dense, thickened cortex with coarse trabeculations is characteristic of the advanced disease.

DISCUSSION

The dense overgrowth of bone with bowing of the long bones and coarse trabeculation occurring in osteitis deformans is easily recognized in the roentgenogram so that in most instances the diagnosis can be made with little difficulty. The osteolytic phase, especially when it occurs alone, is less familiar. S. Moore,[16] writing as early as 1923, stated that there were two processes, rarefaction and condensation going on side by side. A year later Sosman[21] reported a case exhibiting the peculiar circumscribed are of osteoporosis of the skull previously described by Schüller. This was biopsied by Cushing and the sections were interpreted by Wolbach as Paget's disease.[22] Sosman interpreted this as simply the destructive phase of Paget's disease without the productive phase and described the lesion as monophasic Paget's disease. This interpretation was verified a few years later when Kasabach and Dyke[13] reported a transition from osteoporosis circumscripta to classical Paget's disease, and in 1937 Kasabach and Gutman [14] collected 47 cases in the literature. It seems firmly established that in the bones of the skull, at least, the processes of bone decalcification and bone production do not necessarily occur simultaneously.

Recognition of the monophasic process in the long tubular bones has not been as commonly recognized. In their studies of 116 cases of osteitis deformans, Kasabach and Gutman found no sharply defined areas of osteoporosis definitely identifiable as osteoporosis circumscripta, except in the skull. However, Kasabach and Dyke, Meyer-Borstel, and Brailsford have all reported examples of this form of Paget's disease in the tibia.

The pathological physiology of the disease has been lucidly explained by Albright and Reifenstein[1] who agreed with Schmorl that the process is a localized bone disease and stated that the increased bone formation was the result of increased bone destruction. Schmorl[20] demonstrated this by taking a section of bone 2 centimeters distal to the point of gross involvement and proving that the initial lesion in the long bones was bone resorption. He showed only bone destruction without any evidence of bone formation. Albright and Reifenstein further stated that mechanical stress stimulates the osteoblasts so that bone repair occurs almost simultaneously with bone destruction because of the stress and strain to which they are constantly subjected. They explained the presence of osteoporosis circumscripta in the skull by the absence of this constant stress and strain which allows the processes of resorption and bone formation to be divorced. This is by no means invariable, as shown by Dickson *et al.* who found osteoporosis circumscripta in only 26 of 117 cases of Paget's disease of the skull. Occasionally the appearance of long bones may suggest some separation of the two processes. These authors described two forms of osteitis deformans involving the tibia, the earliest of which they termed "acute halisteresis." One of their illustrations demonstrated two separate zones of localized osteoporosis in the upper and lower ends of the tibia, but not the expansion of the anterior cortex as demonstrated in Cases I and II described above. Albright and Reifenstein reproduced roentgenograms from a case in which the advancing

edge of a tibial lesion of Paget's disease was osteoporotic. In the case reported by S. Moore, the distal end of the tibial lesion has the appearance of a rarefied expansion of the anterior cortex of the tibia and resembles the tibia of Case 1, described above.

No explanation has been forthcoming as to the infrequent predominance of the osteolytic phase of Paget's disease in the appendicular skeleton or to explain its being limited to the tibia in the few reported cases.

SUMMARY

A report of two cases of expansile, osteolytic lesions of the anterior cortex of the tibia occurring in young males is presented. One was followed for thirteen years and developed a dense, thickened cortex with coarse trabeculations characteristic of Paget's disease. The other had a few coarse trabeculations in the adjacent bone when first seen. This seems to substantiate the opinion of many that the initial change in the pathogenesis of Paget's disease is bone resorption.

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ADDENDUM

Recently in a report by L. Tavernier, *Lyon chir.*, April, 1950, *45*, 275–280 (1950 Year Book of Radiology, p. 96), a patient was described who had several cyst-like defects in the anterior aspect of the mid-shaft of the tibia. One year later the tibia showed the typical changes of Paget's disease. The reproduction of the roentgenograms is very similar to the cases described above.

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A CASE OF GENERALIZED OSTEOSCLEROSIS*

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THE following is a report of an apparently systemic disease, chiefly localized to the bones and manifesting itself as a generalized osteosclerosis, with a number of organic symptoms which perhaps must be considered part of the clinical picture. It has not been possible on the basis of the literature that is generally accessible to fit the clinical picture into any of the known osteodystrophies, not even the atypical ones; therefore, we thought that the publication of the case might be of interest. We have attempted to explore the case by the available methods of examination but have, however, confined ourselves to those most necessary to the entity.

At the end of the paper we shall mention the differential diagnostic discussions on the known osteodystrophies.

The patient was a female, married, aged forty-one. She had been referred to the otolaryngological clinic by a local prosthodontist whom she consulted without any view to her present disorder, but because one of the front teeth in her lower denture had broken. It may be mentioned that otherwise the function of the denture was completely satisfactory. The prosthodontist then discovered "a couple of cartilage nodes" on the lingual side of the mandible at the level of the incisors; as he was unable for this reason to fit the denture, he advised the patient to be examined and, if necessary, treated at the otolaryngological clinic.

The preliminary diagnosis was systemic disease of the bones, and the patient was admitted to our department for examination.

The objective examination showed the following:

The appearance of the patient is by no means extraordinary; apart from a fairly large skull with an over-dimensioned mandible, a somewhat stooping carriage and a slightly oblique and cautious gait, there seemed at first glance to be nothing in particular that differed from the normal. Her appearance was corresponding to age. Height 164 cm., weight 68 kg.; state of nutrition, medium. No jaundice or cyanosis. Temperature on admission: 37.5° C. (during the period of observation she was subfebrile, temperature $<38°$ C.). Pulse rate 80, respiration 20.

Skull: The entire skull was symmetrically enlarged, except for the mandible which was

FIG. 1

monstrous and displayed an enormous prognathism. In particular the base was greatly and uniformly enlarged, up to 3 cm. The ramus was distinctly elongated but not correspondingly thickened. On the lingual side, at the level of the lower incisors, there were two smooth, hard, bony protuberances the size of hazelnuts, covered by normal mucous membrane; she had a full denture. All the bones of the skull were smooth, uniform, hard to the touch, without any palpable localized thickening of any bone, especially in the calvarium. The occipital protuberance was not distinctly enlarged nor were the superciliary ridges. The sutures were apparently normal, closed like the fontanelles.

The external ears, the nose and lips were normal.

Otherwise the skull was not deformed.

Eyes: Movements normal, pupils normal, round, of equal size; they react normally to

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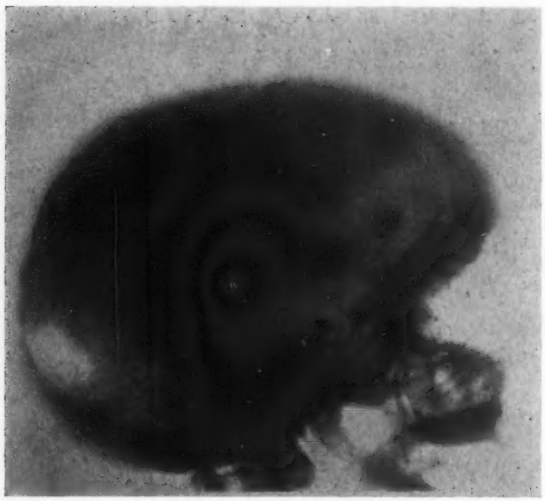

Fig. 2

light and convergence; no exophthalmus or other symptoms of Graves's disease.

Oculist's examination: V.o.u. 6/6 Em. The refracting media clear. Pupils normal. Ophthalmoscopy normal. Field of vision: white 1/330 and 2/1,500, and red 5 and 2/1,500, normal. No suspicion of hemianopsia. There is homolateral diplopia when the patient looks to the left.

Diagnosis: Paresis n. abducentis sin. (Dr. Diemar).

No palpable peripheral glandular swelling.

Thyroid gland: Both lobes moderately enlarged, of a uniform rather hard, very slightly rugged consistency. No palpable thrill or abnormal pulsation. The skin covering the gland is normal, without any abnormal vein markings. The gland can be moved normally with the larynx.

Stethoscopy of the heart: No voussure, no fremitus. Action regular. Pulse rate 80. No accentuations. A continuous systolic see-saw murmur is heard over the entire precordium, most pronounced at the left sternal margin.

Stethoscopy of the lungs: No abnormal sounds, or dullness. Large kyphoscoliosis in the entire thoracic column, sinistroconvex, with its vertex at the level of the lower thoracic vertebrae. The lumbar lordosis partly straightened, with a slight scoliosis to the right.

Abdomen: Normal, no palpable enlargements of the organs.

Extremities: Both the upper and lower extremities were quite normal to look at and to the touch; straight, rather gracile; in particular her hands and feet were rather small. Muscular strength good. Tonus normal. Movements normal. The patient stated that the sensitivity to touch of the skin of her left hand had decreased (was said to be due to a trauma of her left elbow in a fall from a carriage about ten years ago); the remaining neurological examination showed nothing abnormal; no tremor.

Reflexes: Normal.

A.d.+s.: Normal. Hearing normal (V. $\frac{8.00}{8.00}$).

Mastoid region: Normal.

Nasal cavity: Normal, unobstructed passage of air; accessory sinuses: nothing abnormal.

Nasopharynx: Normal.

Pharynx: Rather normal; tonsils, however, slightly hypertrophic, not adherent. Detritus, but no coating.

Larynx: Normal. Vocal cords normal, moving normally.

Skin: Normal, warm, but not moist. No dermography, no edema, thickening or discoloration; growth of hair normal, of feminine pattern. Hair of the scalp not especially thin or gray.

Extract of anamnesis: The patient has previously been in the surgical department of this hospital on two occasions; in 1934 for "ap-

Fig. 3

pendicitis," not operated on, and in 1945 for "hemorrhoids"; surgical operation. Otherwise she has, on the whole, been in good health previously. Has not had diphtheria, scarlet fever or rheumatic fever. No known cases of tuberculosis or "cancer" in the family. Never any diseases of the ear. Adenoids and tonsils not removed. Has not been suffering from frequent acute tonsillitis. Two normal parturitions, in her home, nineteen and sixteen years ago. Immediately after the last child was born it was admitted to the surgical department of this hospital where it died of myocele. The first child is normal and of natural development. The patient menstruated normally until a few years ago when bleeding became more copious, of eight days' duration and irregular, up to three times monthly. Has not been treated for this. No congestions or episodes of perspiration. Her libido has remained unchanged. She has not observed any changes of the pubes.

Her present disorder must be supposed to have developed slowly during the past ten years or so, without being noticed by the patient herself or others, as no changes in her appearance had been observed. She said that she had no subjective symptoms at all which might be attributed to her present disorder, and that she had never had any. She has not had any headache or disturbances of vision, nor has she noticed any impairment of vision. The patient had not noticed any increase of the circumference of her skull; she never wears a hat. Further, she had not noticed any appreciable change of her height or weight. Her feet had not grown, as she took the same size of shoes as she did when she was confirmed. Her

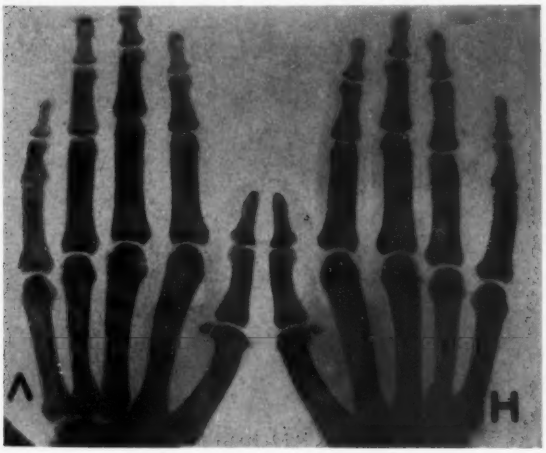

Fig. 4

Fig. 5

hands had not grown. She had not felt tired or depressed. No nervousness or night sweats. She had not been troubled by nasal stenosis or excessive lacrimation. Her hair had not become gray or thin. The patient thought that during the past ten years or so she had noticed an increasing curvature of the spine. "For many years" she had had periodic "rheumatic pain" in her back, localized in particular to the lumbar region. However, she was still able to carry and lift heavy things. She had not noticed any acroparesthesia. Muscular strength apparently good. Never any cardiac or pulmonary symptoms. No dyspepsia; her appetite had remained good. Micturition normal, no pollakisuria or polyuria. No undue thirst. Stools normal, of normal consistency and color. Further, she had not noticed any febrile periods.

Examinations in the Department:

Roentgenography: The entire skeleton displayed in all the bones a vigorous uniform sclerosing with partly obliterated medullary cavities; the external contours were almost smooth.

The skull was strikingly "dense," almost impervious to roentgen rays. The cranial wall was extremely thick, measuring from 2 to 3 cm. on the roentgenogram; the bones were sclerosed

Fig. 6

and eburnated, a change that involved not only the cranial bones but also those of the face and the base of the skull; in particular, the mandible was broad, dense and large; it had assumed quite a monstrous form. The pituitary fossa was of normal shape and size (9 by 14 mm.).

The pelvis displayed marked sclerosis but normal shape and size.

The spine showed rather a marked sinistroconvex kyphoscoliosis and a corresponding dextroconvex scoliosis in the lumbar region. The bones were somewhat eburnated but not of the appearance characteristic of "marble bone disease" or Paget's disease. It was also striking that the dense vertebrae yielded to pressure and formed a scoliosis caused by the weight of the body.

Both lower legs and hands, for example, displayed dense bones, producing a dense shadow in the roentgenogram, with partial obliteration of the medullary cavities and sclerosing of the spongy tissue. This applied especially to the proximal half of the tibia. In the hands it was especially marked in the phalanges.

Roentgenography of the thorax showed that the skeleton was very "dense"; in particular, the ribs were very broad and the sternum was prominent. There was nothing abnormal in the roentgenograms of the lungs. Owing to the marked scoliosis, the shape and size of the heart could not be estimated with certainty, but it did not seem to be abnormal.

Roentgenography of the skull of the patient's daughter (aged nineteen) showed nothing abnormal. There was no thickening of the cranial wall and the pituitary fossa was normal. On the whole, she seemed to be normal (H. Christiansen, senior roentgenologist).

Other examinations: Sedimentation rate 21 mm. in one hour; Wassermann reaction negative; blood pressure 140/90; metabolism 118 per cent; electrocardiogram: slight changes, indicative of myocardial degeneration. Urine: no albumin, no sugar; microscopic examination of urine: nothing abnormal; output of urine: 600 to 950 ml.; specific gravity 1.031–1.029. Fasting blood sugar 83 mg. per cent; blood urea 69 mg. per cent; serum calcium 9.3 mg. per cent; serum phosphorus 3.3 mg. per cent; serum phosphatase 2.6 Buch units. Hemoglobin 83 per cent, red blood cell count 3.9 million, color index 1.06, volume per cent 28, volume index 0.81, white blood cell count 6,300, reticulocytes 0.8, blood platelets 230,000, plasma color figure 4. Differential count: neutrophils 54 per cent, eosinophils 1 per cent, basophils 0, lymphocytes 38 per cent, monocytes 7 per cent; no myelocytes, myeloblasts or lymphoblasts. Otherwise no abnormal forms. Red blood picture, normal.

Differential diagnostic considerations

The disorders which it will be most natural to consider and which should be first and foremost distinguished from the present clinical picture are the so-called osteo-

Fig. 7

dystrophies. The most obvious one is "osteitis deformans, Paget." However, there seem to be essential differences. Paget's disease generally affects patients over forty years of age; and frequently, the bones of the extremities are first attacked, and especially the tibia which becomes greatly deformed macroscopically at an early stage. The medullary cavities become distended. In the roentgenogram there will be seen a lamellar structure of the compact layers and a coarse, in many cases very distinct, mosaic structure with insular, osteosclerotic areas in an otherwise osteoporotic matrix. Attention should be paid to the fact that the serum phosphatase is increased, even more than in osteitis fibrosa; pain in the extremities is generally also an essential symptom. As far as we know, the phalanges are never affected. Pigmentations of the skin covering the affected parts are often seen. The contours of the calvarium most frequently display a peculiar, roughly serrated or undulated appearance, "a woolly appearance." Completely normal bones are found simultaneously with the pathological bones.

Albers-Schönberg's "marble bone disease" sets in at a much earlier age and dates back to childhood in most cases; it affects the ends of the long bones in particular; the roentgenograms display a very characteristic marble appearance and fractures are of frequent occurrence. In many cases the disease is associated with splanchnomegaly. Melorheostosis manifests itself as a hyperostosis which only affects the outer contours of the long bones.

Fluorosis is out of the question in this case. It appears as a diffuse osteosclerosis and calcifications of the ligaments, especially in the spine and the pelvis.

Osteopoikilosis is a localized affection occurring especially around the joints.

We may add for completeness that such a generalized osteosclerosis has never been observed in acromegaly.

CONCLUSION

This was the case of a woman, aged forty-one, suffering from a systemic disorder localized to the osseous system and involving all the bones; the condition seems to have been uniformly and diffusely progressing for about ten years. It is remarkable that, apart from rather vague rheumatic sensations, the patient has been almost free from symptoms; of symptoms of cranial pressure she only developed a paresis of the abducens. Considering the fact that all the bones were greatly sclerosed and the medullary cavities were much reduced everywhere, even quite obliterated in parts, it was strange to find only a slight hypochromatic anemia which must *eo ipso* be termed osteosclerotic. Whether her goiter with the slightly increased metabolic rate, and the unquestionable cardiac disorder, should be considered part of the clinical picture, must be left undecided. It may be mentioned that her sedimentation rate was increased, but that there were no signs of any present infection or of one that had occurred recently. It may be stressed that calcium, phosphorus and phosphatase in the serum showed completely normal values. The increased blood urea does not fit into the picture, as the other examinations of the urine were normal, but it is stated for completeness. The patient did not have signs of thyrotoxicosis. It goes without saying that the etiology has not been cleared up, and any therapy can hardly be considered; it seems hopeless in advance to attempt palliative roentgen therapy.

SUMMARY

The writers report the case of a generalized osteosclerosis, affecting all parts of the skeletal system in a middle-aged woman. The disease seems to have been developing for about ten years. Apart from some slight rheumatic pain, the patient has been free from symptoms. The investigations showed roentgenologic signs of sclerosis quite different from any known osteodystrophy.

Apart from a slightly degenerated myocardium, a small goiter, without toxic symptoms, and a paralysis of the left abducent nerve, nothing pathologic has been found. The blood showed nothing abnormal, except for a simple hypochromatic anemia;

in particular, the content of calcium, phosphorus, and phosphatases proved quite normal.

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GASTROILEOSTOMY

CASE REPORT

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GASTROILEOSTOMY is an unusual surgical error. A brief review of the current literature reveals only 26 cases reported up to 1947. No references were found in the American radiological literature.

CASE REPORT

J.T., a white male, aged twenty-eight, was admitted to the Palo Alto Hospital in April, 1948. Briefly, he presented a nine year history of nausea, vomiting, and recurrent episodes of hematemesis. Nine years previously a pyloroplasty had been done at another hospital and the patient was told that he had a duodenal ulcer. In 1943, a gastroenterostomy had been done elsewhere. His symptoms continued unchanged. In 1947 a gastrointestinal series was done elsewhere. The conclusion at this time was "malfunctioning gastro-enterostomy with possible fistulous communication between the small intestine and colon." Gastric resection was recommended but refused.

On admission to this hospital his principal complaints were severe generalized muscle cramps, carpopedal spasm, nausea and vomiting. The clinical impression was intestinal obstruction, alkalosis and parathyroid tetany.

After correction of his electrolyte balance and consequent relief of his major complaints, roentgen examination was done.

Roentgen examination of the upper gastrointestinal tract revealed a moderately dilated stomach. Only a little barium passed the pylorus and the duodenal cap could not be outlined. There was a poorly functioning gastroenterostomy, the stomach communicating with a loop of small intestine by a narrowed and elongated tract about 5 cm. in length and not over 5 to 7 mm. in diameter. The small intestine was markedly dilated, measuring 9 cm. in its greatest diameter (Fig. 1). This loop extended from the upper mid-abdomen to the right lower quadrant. The contour suggested it was ileum, although the size and position simulated ascending colon. Normal jejunum was subsequently identified in the left upper quadrant, slowly being filled via the duodenum. The stomach emptied very slowly, retaining a large amount of barium at six hours. Throughout the examination, what appeared to be ascending colon containing gas and fecal material could be identified lateral to the dilated

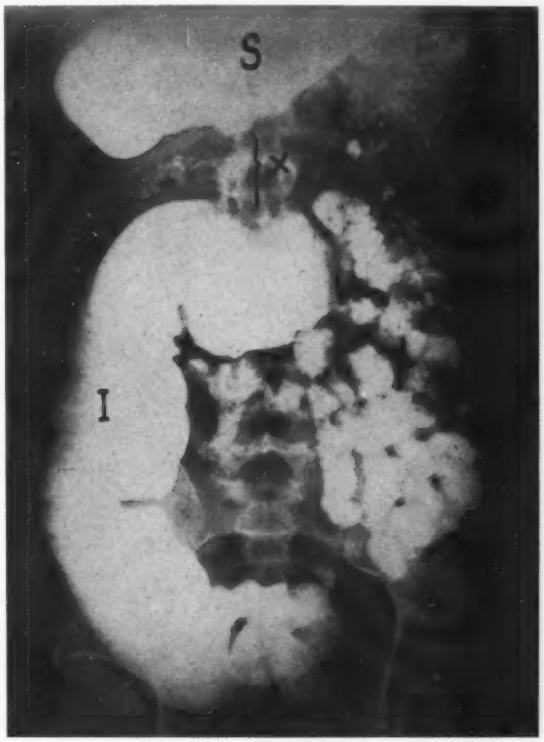

FIG. 1. Film of abdomen, six hours after barium meal, showing dilated stomach (*S*), gastroileal communication tract (*X*), normal jejunum (*J*), and dilated proximal limb of ileum (*I*).

loop of small intestine. Even at six hours, no barium had entered the colon. Subsequent examination by barium enema revealed a normal colon. A line drawing (Fig. 2) shows the course of the barium meal.

At operation, the ileum was found anastomosed to the stomach approximately 2½ feet proximal to the ileocecal valve. There was a

stomal ulcer in the ileum with surrounding inflammatory reaction, binding it to the transverse colon. The dilated segment of ileum was the proximal limb of the loop. The pylorus and first portion of the duodenum were markedly deformed by scar tissue. The gastroileostomy

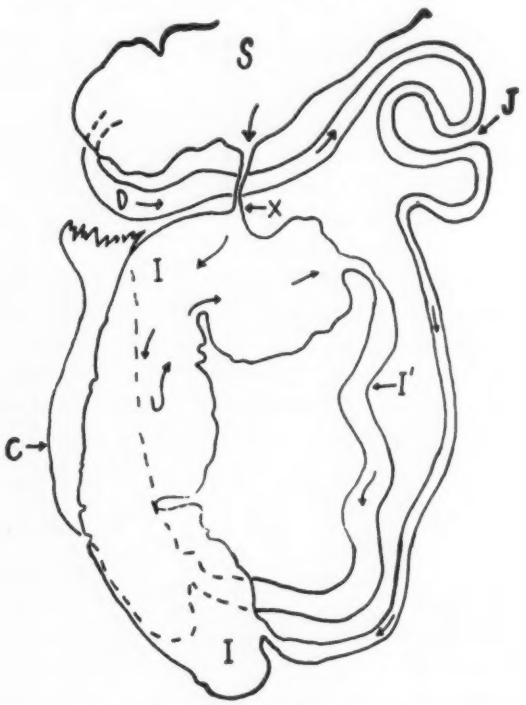

Fig. 2. Line drawing showing course of intestinal stream. Stomach (*S*), duodenum (*D*), gastroileostomy (*X*), jejunum (*J*), proximal dilated limb of loop of ileum (*I*), distal limb of loop of ileum (*I'*), ascending colon (*C*). Arrows indicate course of intestinal contents.

was taken down and the opening in the ileum was closed. A Polya type gastric resection was done. The postoperative course was dramatic in the rapidity with which the patient gained freedom from his previous gastrointestinal complaints and he continued free of symptoms when last seen two months after the operation.

The actual incidence of gastroileostomy is difficult to determine, inasmuch as many that occur are probably not reported. While the common symptoms are nausea, vomiting, weight loss, pain, and diarrhea,[1,2] no pathognomonic clinical picture is presented. The present case did not exhibit diarrhea and weight loss was not striking. The absence of diarrhea is probably explained by the stasis in the proximal limb of the ileal loop and the intestinal contents were actually delayed in reaching the colon. Brown *et al.*[1] described refilling of the stomach if some barium leaves the stomach by way of the pylorus and duodenum. Such did not occur in this case, undoubtedly because of the narrowed and elongated communication between the stomach and ileum.

SUMMARY

A case of gastroileostomy, performed erroneously, is presented. The condition has no pathognomonic clinical picture. In cases of malfunctioning gastroenterostomy, the roentgenologist can make an accurate and helpful preoperative diagnosis, if aware of the possibility.

The author is indebted to Dr. Blake C. Wilbur, Dr. J. Sewall Brown and Dr. John L. Anderson for clinical information used.

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Vol. 66, No. 4

THE VALUE OF VENTRICULO-ENCEPHALOGRAPHY IN PLANNING ROENTGEN THERAPY FOR BRAIN TUMORS*

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SINCE 1914 we have been intensely interested in the treatment of brain tumors, pituitary tumors and metastatic malignant lesions of the brain. Yet, for the most part, the evaluation of the effect of irradiation has depended upon the observations made at postmortem examinations years or months after irradiation, subsequent operation, or changes in the clinical picture. We believe that the inadequacy of such observations is largely responsible for the difference of opinion that exists among neurosurgeons as to the value of irradiation in brain tumors.

It is the purpose of this paper to tell of our experience with ventriculo-encephalography in planning roentgen therapy for brain tumors. The term ventriculo-encephalography is used to include those patients in whom the procedure of encephalography and ventriculography was carried out simultaneously. This idea in part has been considered by others, in fact, Dyke and Davidoff[1] published two illustrations of encephalograms in their book which illustrate the appearance of an eosinophilic pituitary adenoma before treatment and the disappearance of the mass eleven months after roentgen therapy.

According to our present knowledge, there are no contraindications to the procedure so far as increased intracranial pressure is concerned. The patient is taken to the operating room where air is introduced into the ventricles through trephine openings and into the subarachnoid space by way of a lumbar puncture, following which roentgenograms are made in the erect and horizontal positions.

We recommend ventriculo-encephalograms in every patient who is to receive roentgen therapy. They are valuable in showing the changes following operation, the size and position of the lesion, the appearance of the ventricles and subarachnoid spaces, and, most important, they provide a base-line from which conclusions as to the effect of treatment may be drawn. With such information one can plan the number and size of the portals essential to irradiate the lesion without necessarily including all the normal brain tissues. It is the only method now available which allows one an opportunity to estimate the amount of radiation directed into the lesion. Without such information it is impossible to evaluate effects of irradiation on brain tumors. Unless ventriculo-encephalography is utilized, one must treat the entire brain or run the risk of not including all of the lesion or lesions. Without accurate localization of the tumor one usually employs large portals; the radiation is directed perpendicular to the skin surface of the head without adequate knowledge as to the extent of the lesion, with the result that in some instances enough radiation is administered to produce radiation necrosis of bone; yet the major portion of the radiation was not directed into the lesion.

Despite our enthusiasm, our material is limited. It is hoped that a report of our experience may stimulate others to join us in the effort to test the value of roentgen therapy of brain tumors as observed by ventriculo-encephalography. Some of the cases treated by us are reported as follows:

[1] Dyke, C. G., and Davidoff, L. M. Roentgen Treatment of Diseases of the Nervous System. Lea & Febiger, Philadelphia, 1942, pp. 143–145, Fig. 6 and Fig. 7.

* From the Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Presented at the Fifty-first Annual Meeting, American Roentgen Ray Society, St. Louis, Mo., Sept. 26–29, 1950.
† Fellow of the American Cancer Society.

REPORT OF CASES

CASE I. J.S., female, aged twenty-three, admitted December, 1940, for diplopia, slight ataxia, vertigo, and headache of slight degree of one month's duration. The neurological examination revealed inability to balance properly on the left leg, right past-pointing, handwriting defect, bilateral choked discs, and paresis of the right internal rectus muscle. The spinal fluid pressure was 450 mm. of water. Roentgenograms of the skull showed evidence of increased intracranial pressure.

A ventriculographic study (Fig. 1, *A*, *B* and *C*) on January 6, 1941, showed a mass slightly to the left of the midline in the frontoparietal region. A right frontoparietal bone flap was raised; the cortex looked normal; a transcortical incision was made into the anterior horn of the right ventricle, bringing the operators down

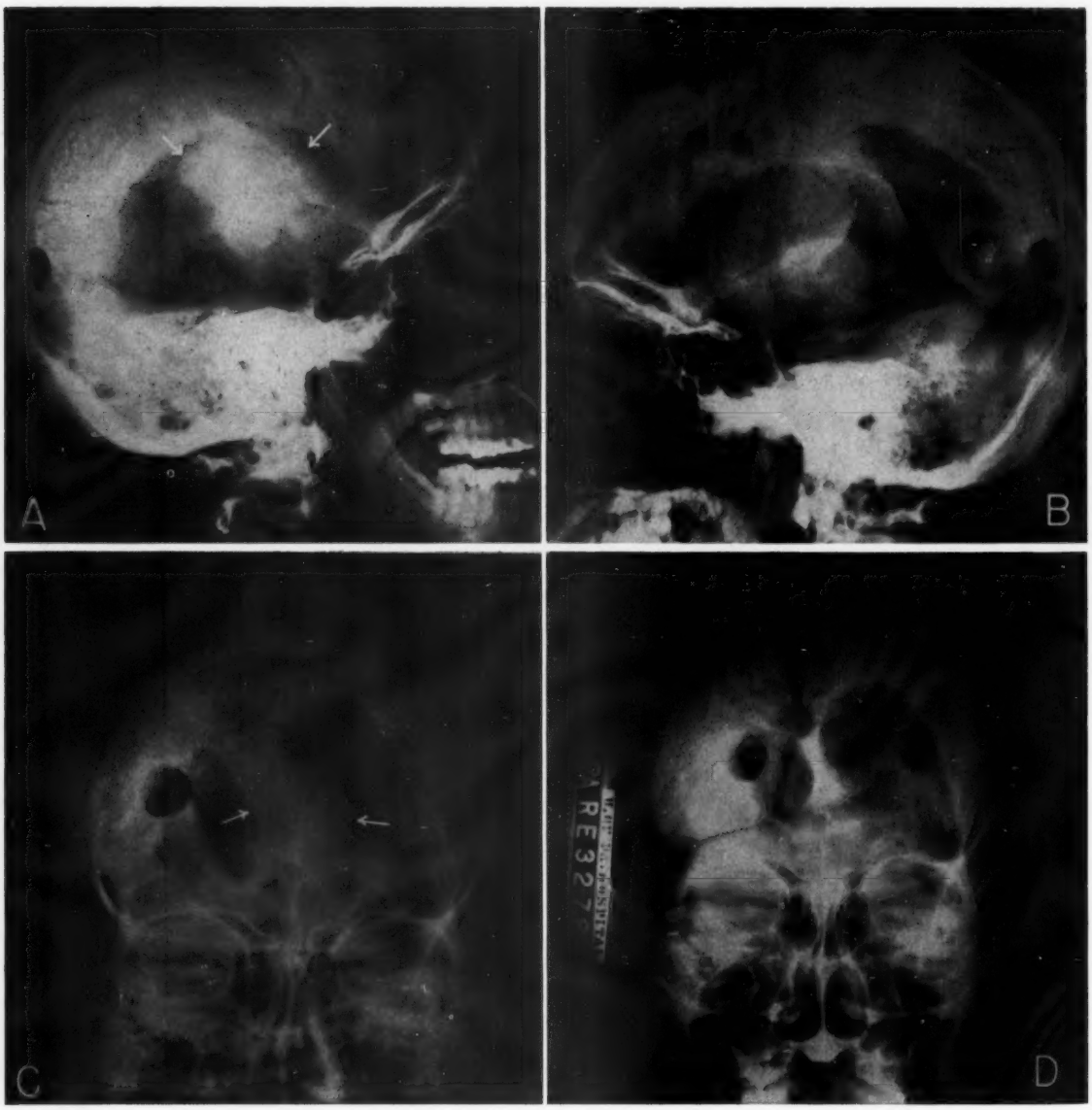

FIG. 1. Case I. (*A*) The left lateral ventriculogram made on January 6, 1941, shows a large tumor (outlined by arrows). (*B*) The right lateral ventriculogram shows a large pressure defect of the left ventricle. (*C*) A posteroanterior ventriculogram shows the midline tumor (outlined by arrows). (*D*) The ventriculogram made on June 18, 1941, three months after roentgen therapy, shows a marked reduction in the size of the tumor.

on a tumor which seemed to lie in the third ventricle and in part of the anterior horn of the right lateral ventricle. It was reddish, infiltrating and vascular. A frozen section of a small piece of the tumor was full of cholesterol crystals and it was suspected of being a craniopharyngioma. An exploration of the pituitary region revealed nothing abnormal. Interventricular drainage was established behind the point of the lesion. Subsequent microscopic examination showed no evidence of tumor in the specimens removed.

As the tumor had not been removed, the patient returned for roentgen therapy in March, 1941. Three months later a ventriculogram (Fig. 1*D*) showed that the lesion was markedly reduced in size and there was amorphous calcification in it; the tumor dose had been 3,670 r.

The patient continued her normal activities without disability. She was followed up periodically and has had frequent skull examinations, and at least four subsequent ventriculographic studies over a period of years. The lesion calcified and became smaller. The dilatation of the ventricular system disappeared.

For the past few years, very little change has been noted. She has no neurological signs, and held a position when last heard from in July, 1950.

Case II. O.B., male, aged eighteen, first admitted July 30, 1943, because of frontal headaches, projectile vomiting and a staggering gait. Ventriculograms showed definite evidence of a lesion in the fourth ventricle. At operation a tumor was removed from the roof of the fourth ventricle. Microscopically the lesion was a medulloblastoma.

The patient's symptoms improved postoperatively, but after three months the cerebellar signs increased again. The patient was treated over the cerebellar region through four portals and the entire spinal cord through three portals. This treatment resulted in an improvement of all his symptoms, especially his gait, diplopia, and headaches. A ventriculoencephalogram made eight months later to check the size of the lesion showed reduction in size of the ventricular system, except for the fourth ventricle which was enlarged with a recurrence of the tumor. There was a large collection of air at the base suggesting a subarachnoid or porencephalic cyst (Fig. 3, *A* and *B*). More roentgen therapy was given to the cerebellar region through occipital and vertex portals. Slight improvement followed this treatment.

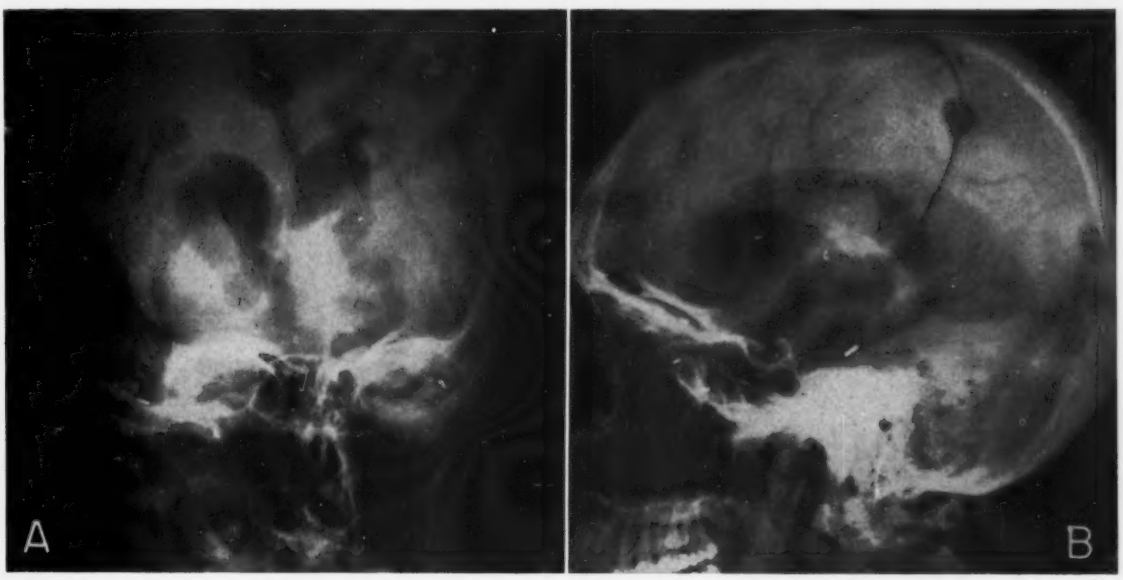

Fig. 2. Case I. (*A*) The posteroanterior ventriculogram, January 26, 1946, shows that the dilatation of the ventricles has disappeared (compare with Fig. 1*A*). (*B*) The right lateral ventriculogram shows very little residual evidence of the tumor.

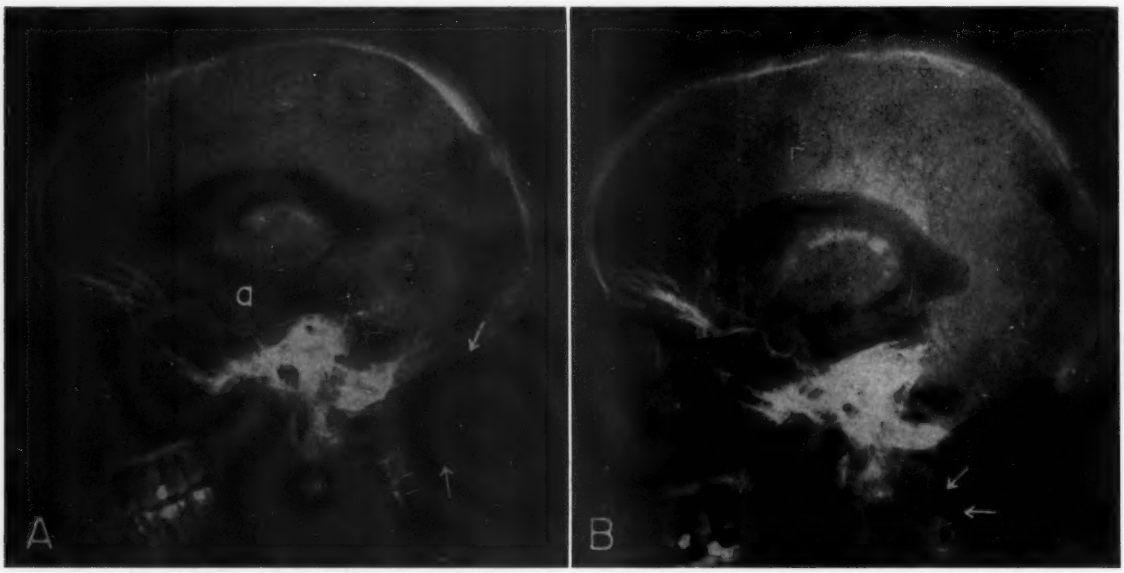

Fig. 3. Case II. (*A*) A ventriculo-encephalogram made in the erect posture. This examination was made eight months after the completion of the roentgen treatment. Very few symptoms were present. One can see the normal lateral and third ventricles. We were concerned about the opaque shadow in the dilated fourth ventricle (outlined by arrows). If this view alone had been relied upon, one would conclude that the fourth ventricle was filled with tumor and had difficulty in explaining the lack of dilatation of the remaining ventricular system. Note the air-filled cisterna pontis at *a*. (*B*) The ventriculo-encephalogram made in the horizontal posture of the same patient shows a large air-filled fourth ventricle. There is a small nubbin of tumor outlined by arrows. The shadow seen in the fourth ventricle in the erect posture is due to cerebrospinal fluid. Utilization of studies made in the erect and horizontal postures enables one to obtain more information than is otherwise possible.

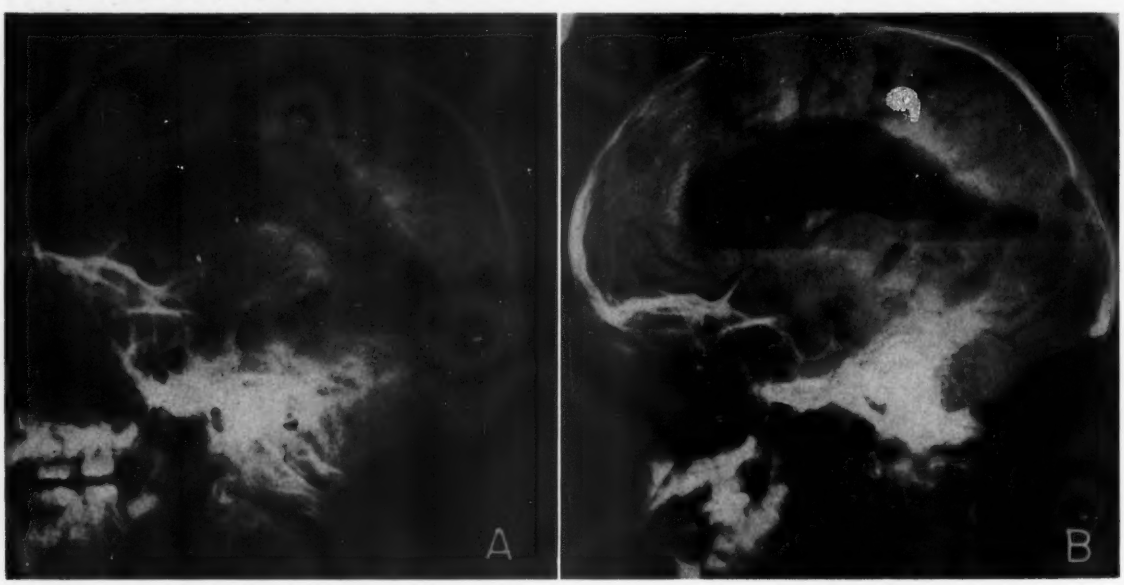

Fig. 4. Case III. Ventriculo-encephalograms made in the horizontal (*A*) and erect (*B*) postures show dilatation of the lateral and third ventricles. The large posterior fossa lesion completely obliterates the fourth ventricle and subarachnoid pathways. It would have been impossible to obtain a comprehensive study of this lesion without the combined air study.

On June 22, 1945, another ventriculo-encephalographic study showed a large recurrence in the fourth ventricle and seeding to the third ventricle. Two portals were used to treat the cerebellum and three for the third ventricle lesion. He improved somewhat, but died on September 25, 1945.

At autopsy there was a fungating tumor mass in the caudal portion of the vermis obstructing the exit to the fourth ventricle, displacing the right cerebellar hemisphere to the right, and filling the sulcus between the right side of the medulla and the cerebellum. The spinal cord showed no evidence of seeding.

The total tumor dose for the several series was 12,139 r. The cervical, thoracic and lumbar cord each received 900 r.

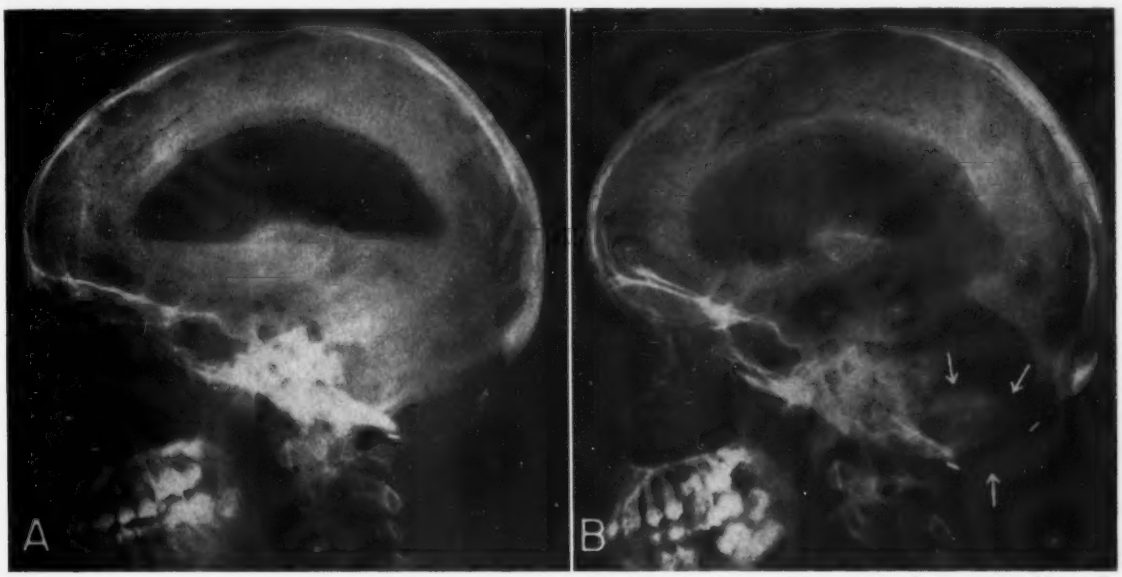

Fig. 5. Case iv. Ventriculo-encephalograms of a ten year old girl with symptoms of increased intracranial pressure made in November, 1944. This examination, two years after completion of roentgen therapy to the cerebellum, shows that in the erect position (*A*) the third and fourth ventricles are not visualized due to undrained cerebrospinal fluid. In the horizontal position (*B*) they are well aerated and reveal a large recurrence in the ependymoma in the fourth ventricle.

Case iii. G.Z., male, aged seven, was first admitted May 19, 1950, because of frontal headaches, unsteady gait, and progressive drowsiness. Neurological examination revealed bilateral papilledema, an occasional nystagmus to the left, a positive Romberg, ataxia, bilateral Babinski, and an ankle clonus. A suboccipital craniectomy was done May 22, 1950, and an extensively infiltrating tumor was found involving the roof and floor of the fourth ventricle, the vermis, and the medulla. No attempt was made to remove the major part of the tumor. Postoperatively he did well and radiation therapy was given from June 3, 1950, to August 18, 1950, through multiple head portals and spine portals. On July 8, 1950, a ventriculo-encephalogram was made (Fig. 4, *A* and *B*); the posterior fossa tumor was demonstrated. On discharge the patient showed definite improvement.

He received a tissue dose of 6,600 r to the center of the tumor, 1,500 r to the lower dorsal and lumbosacral spine, and 1,000 r to the upper dorsal and cervical spine. The pathological diagnosis was medulloblastoma.

Case iv. B.A., female, aged ten, first seen May 18, 1942, with complaints of vomiting, headache, and incoordination of five months' duration. Skull roentgenograms showed evidence of increased intracranial pressure and a calcified posterior fossa tumor. Suboccipital craniectomy revealed a soft, mushy tumor in the vermis. The major part of the tumor was removed, but a portion on the left side could not be completely removed. Microscopically it was an ependymoma.

After several months the occipital flap be-

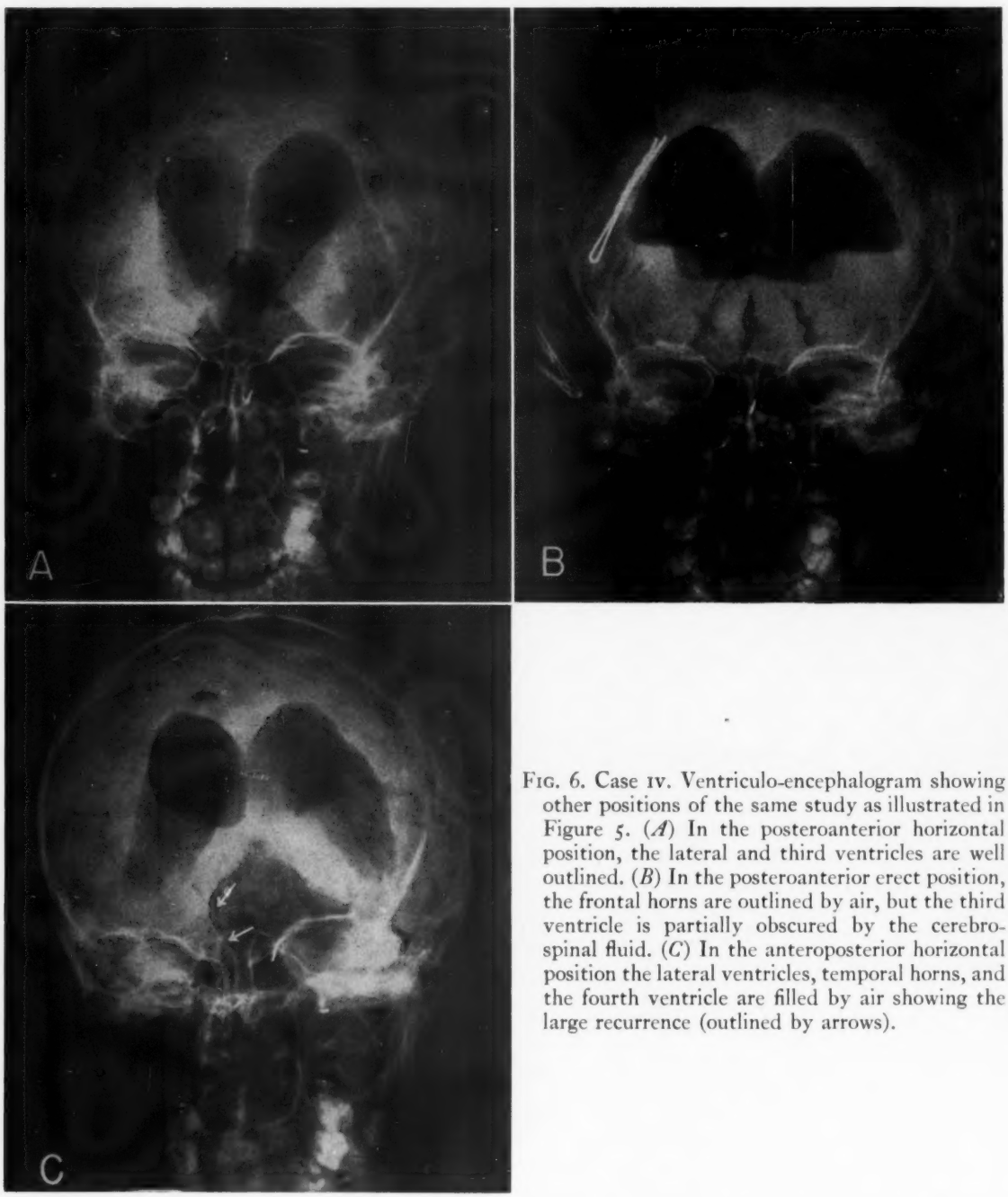

Fig. 6. Case iv. Ventriculo-encephalogram showing other positions of the same study as illustrated in Figure 5. (*A*) In the posteroanterior horizontal position, the lateral and third ventricles are well outlined. (*B*) In the posteroanterior erect position, the frontal horns are outlined by air, but the third ventricle is partially obscured by the cerebrospinal fluid. (*C*) In the anteroposterior horizontal position the lateral ventricles, temporal horns, and the fourth ventricle are filled by air showing the large recurrence (outlined by arrows).

came tight, and ventriculograms in October, 1942, showed generalized enlargement of the entire ventricular system. Roentgen therapy was directed to the residual tumor through three portals. The patient improved.

In November, 1944, the patient was again admitted because of recurrence of symptoms in a more severe form, with vomiting, pain in the back and headache. Ventriculo-encephalograms (Fig. 5, *A* and *B*, and Fig. 6, *A*, *B* and *C*) showed an increase in the size of the ventricles with a huge fourth ventricle containing a tumor recurrence. Re-operation was done and a large, purplish tumor was found involving the vermis and this was partially removed. Microscopically it was ependymoma with reactive scar tissue. The patient was given further roentgen therapy and she improved for several

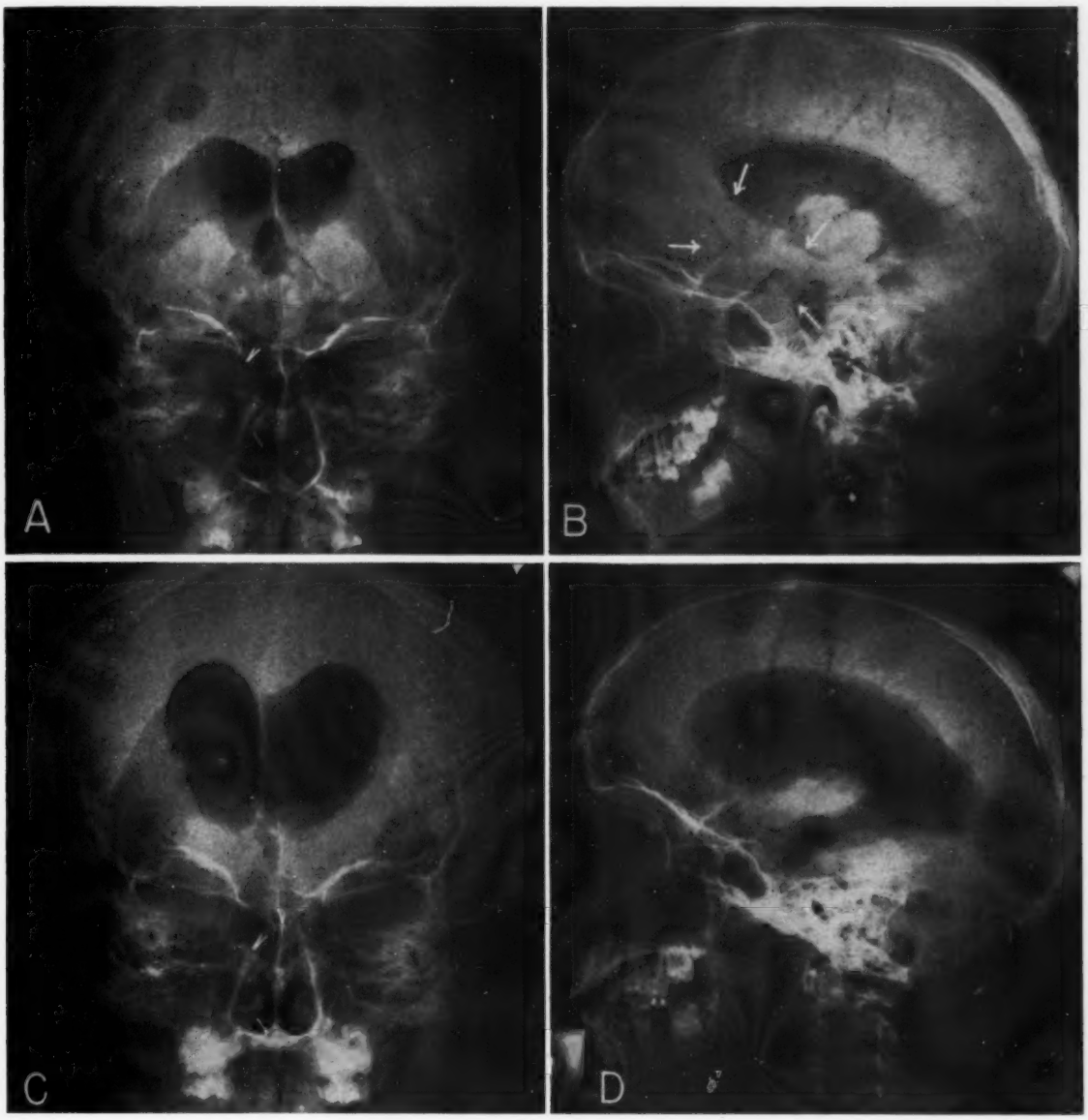

Fig. 7. Case v. Ventriculo-encephalograms were made in February, 1945, nearly three years after the roentgen therapy. In (*A*) there is slight dilatation of the ventricular system. In (*B*) one can see an extensive lesion in the region of the chiasm encroaching on the anteroinferior surface of the frontal horns and the anterior portion of the third ventricle (outlined by arrows). One year later, in (*C*), an extensive recurrence is evident causing marked dilatation of the ventricles. In (*D*) there is extension seen in the dilated fourth ventricle and the obliterated third ventricle.

months. On July 28, 1945, she died at home.

The tumor dose was 5,926 r and the lumbar spine received 915 r.

Case v. W.O., male, aged eight, admitted on May 5, 1942, with headache, vomiting, drooping of the right eyelid, and an 8 pound weight loss. Skull roentgenograms showed evidence of increased intracranial pressure. A ventriculographic study revealed a dilated ventricular system with a block aqueduct, indicating a posterior fossa lesion. At operation a large tumor of the vermis and fourth ventricle was partially removed. The microscopic diagnosis was medulloblastoma.

Roentgen therapy was given to the residual tumor through three occipital portals, followed by a course of roentgen therapy to the entire

spinal cord. The patient remained in good health thereafter until January, 1944, when he developed frontal headaches, vomiting, nystagmus and a positive Romberg. Further therapy was given to the cerebellum through three portals and to the spinal cord. The patient improved rapidly and was all right until February, 1945, when he had several transient periods of unconsciousness. Ventriculo-encephalograms (Fig. 7, *A* and *B*) showed a mass encroaching on the third ventricle and the lateral ventricles anteriorly. Roentgen therapy was given to this region through three portals, following which the patient improved remarkably. He was well until January, 1946, when he again began to have spells of vomiting, frontal headaches, ataxia, and nystagmus. He was referred for further therapy, but since the scalp had already received considerable irradiation another ventriculo-encephalogram (Fig. 7, *C* and *D*) was done to localize the tumor. A large posterior fossa recurrence was found. At operation there was a large recurrence in the midline about 8 by 8 by 8 cm. running high up under the tentorium; the removal was far from complete, but the aqueduct was unblocked. Microscopically it was shown that the treatment had not destroyed the growth infiltrating the cerebellum. Postoperatively he continued to have markedly increased intracranial pressure, and he died on January 28, 1946.

At autopsy there was massive seeding tumor over the entire base of the brain infiltrating all the basilar cisterns. The ventricular system was dilated and the lateral ventricles were lined with tumor seeding. The tumor permeated through the tips of the temporal lobes to appear on the under surface and to extend into the basilar tumor. The posterior part of the third ventricle and the aqueduct were filled with the tumor, as was the fourth ventricle, and from it extended into the base occluding the foramina of exit.

The tumor dose was 7,470 r; the cervical cord received 2,680 r; upper thoracic cord, 2,680 r; lower thoracic cord, 2,250 r; lumbar cord, 2,250 r, and the third ventricle, 1,740 r.

DISCUSSION

Ventriculo-encephalography, when employed in posterior fossa lesions, has a few difficulties which may be easily obviated if the roentgenograms made in the erect posture are carefully compared with those made in the horizontal. Our technique provides for posteroanterior and anteroposterior exposures in the horizontal and erect postures. Lateral views in the erect and horizontal positions are most helpful. Roentgenograms made with the brow up and brow down are important when the horizontal beam is employed.

Lateral views in the erect posture are exceedingly important for determining information about lesions in the region of the cisterna chiasmatis and middle fossa, whereas, in these lesions, one cannot rely on information obtained in horizontal roentgenograms.

The lateral view in the horizontal posture is most informative for lesions in the fourth ventircle and posterior fossa.

In the posteroanterior and anteroposterior roentgenograms, the midline, third and fourth ventricles may not be seen in the erect posture, whereas they are seen in the horizontal roentgenograms. One explanation for these great variations is the lack of complete drainage of the cerebrospinal fluid in many of the posterior fossa lesions, especially those that have been operated upon.

Ventriculo-encephalography, as illustrated in the cases presented here, is nevertheless an excellent method by which to demonstrate the site and extent of most intracranial tumors. It outlines clearly the ventricular system and the subarachnoid pathways, thus rendering it possible to demonstrate lesions which otherwise might not be evident. Implants in the basal cisterns and recurrences and extensions of the tumor, especially in the region of the fourth ventricle and middle fossa, are very well outlined. The presence or absence of air in the subarachnoid pathways can be shown; when absent, it suggests that an arachnoiditis may have occurred, that a recurrence is present somewhere blocking free passage of air, or that filling has been incomplete. When subarachnoid pathways are outlined by air, the amount of brain damage, if present, can be ascertained. A tumor can be very

accurately localized. Small portals can be planned through which radiation can be accurately directed. Such a method assists in preventing over-irradiation to the normal brain tissue.

At present, roentgen therapy of brain tumors, for the most part is restricted to large neurosurgical centers. If the radiotherapists at those institutions knew the site and extent of the tumor, it would be possible for them to plan the therapy, allow the patient to go home, and be treated by the radiologist in the vicinity of the patient's home. Such a plan would relieve the bed-occupancy in hospitals having busy neurosurgical services, in many instances, reduce the expense of patients and their families, and, most important, get the patient home where he wants to be. The factors used in the treatment of these patients were: kv. (peak), 200; half-value layer, 1.1 mm. Cu; filter, 0.5 mm. Cu; distance, 50 cm., and the portals varied in size from 25 to 80 sq. cm.: the number of portals varied from three to seven.

There are other methods of localization such as arteriography and the use of radioactive isotopes, some of which provide assistance for the neurosurgeon, but there is no other method that provides more accurate information in the great majority of instances for the radiotherapist than ventriculo-encephalography.

SUMMARY

Reports on five patients are presented, illustrating the value of information that may be obtained from ventriculo-encephalography, to be used in planning irradiation for brain tumors. This information includes the following:

1. Accurate localization of a tumor or recurrence.
2. Evidence of residual disease following operation.
3. Estimation of the progress or recession of a tumor following roentgen therapy.
4. Demonstration of multiple lesions as in metastatic carcinoma.

Finally, difficulties in technique leading to errors in interpretation are discussed and illustrated.

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DISCUSSION

Dr. Leonard T. Furlow, St. Louis, Missouri. I appreciate very much the honor of being asked to appear before this society to discuss this stimulating paper by Dr. Pendergrass and Dr. Phillips. I assume that my role as a discussant is due to the fact that I am a neurosurgeon, so I will confine my remarks to the neurosurgical principles involved.

Dr. Pendergrass has intimated that the procedure of ventriculo-encephalography is a rather minor affair, and so it is, when one considers the lethal nature of the lesions which he is seeking to accurately localize. On the other hand, from the patient's standpoint, it may be productive of great discomfort, so that only when the patient has symptoms which indicate real trouble is he willing to submit. It entails a shaved head—with *my* patients, a general anesthetic—and in adults almost always three to four days of gradually decreasing headache. The physician who is long in practice soon finds himself using over and over those tools which he uses best. In this fashion I have come to have a great preference for ventriculography over pneumoencephalography. There are several reasons for this—the first being that pneumoencephalography is generally considered dangerous in patients who have obvious evidence of increased intracranial pressure, so that when I expect to find a space-occupying lesion I almost always use ventriculography. Encephalography alone in my hands is not always diagnostic, for ventricular filling may be poor and I am much less adept in detecting abnormalities of the subarachnoid channels than of the ventricles. In addition, it increases greatly the patient's discomfort because of the added amount of gas which is injected. I would therefore prefer ventriculography alone except in those cases in which a lesion of the pons or of the chiasmal region is suspected. In these instances visualization of the basal cisternae and estimation of the size of the pons may be invaluable. Our usual practice, therefore, has been to localize the lesion initially by ventriculography and determine the need for further therapy on clinical signs which may be either those of increased pressure or of a focal nature.

I must confess that I have become discouraged to the point of no longer using radiotherapy in the glioblastoma group. This is a subject which occasioned much discussion in my former days with Dr. Sachs. I am convinced that the use of large decompressions prolongs life to no useful purpose, for in my days in the Navy I was forced to live with several of these patients to the bitter end. My present method is to remove all of the tumor possible—doing a block resection if the lesion is in a resectable part of the brain—and then closing the dura tightly so that when the inevitable recurrence comes it may be swift in action.

Dr. Pendergrass has some excellent results from roentgen therapy, but I see that he has had his disappointments also. His second case, in which no tumor was present in the tissue removed at operation, but who has now gone ten years with evidence of calcification in the lesion, is probably an oligodendroglioma for these tumors are often very slow in growth and well known for their tendency to calcify.

I would commend the authors for continuing to look for methods which may be of aid in the treatment of these cases, for it is obvious that the methods commonly employed are not too successful. About twelve years ago, Drs. Sachs, Moore and I became enthusiastic about the treatment of these patients through the open wound at the time of operation, giving up to 6,000 r to the tumor bed, but, like radon seeds and the radium bomb, it was given up because it did not work. Only by trial can new methods be evaluated, and all neurosurgeons are convinced that there is much room for improvement. Under present conditions the neurosurgeon must be philosopher as well as surgeon, if he is to remain active in his field. My present belief is that the vast majority of brain tumors may be cured only by complete removal, but this radical removal should be attempted only if one may reasonably expect to salvage a patient who may be economically independent and socially acceptable. This, of course, places definite restrictions upon one's action in the operating room. I am, on the other hand, much opposed to the routine use of biopsies either by needle, or by the removal of a small bit of tumor at operation, for I believe that surgery will, for a long time to come, constitute the chief hope of these patients. Treatment by radiotherapy, without accurate microscopic diagnosis is also to be condemned, for one cannot accurately predict pathology from clinical history. I have just recently removed a benign, encapsulated meningioma from a patient who had had symptoms for only seven days. The problem is large, and our combined efforts are essential for its ultimate solution.

Dr. Pendergrass (closing). I do want to thank Dr. Furlow for his discussion. The discussion he has brought out today is one which the majority of his colleagues (neurosurgeons) would emphasize.

We, as radiologists, are asked to treat patients with brain tumors and metastatic malignancy and oftentimes we are asked to treat them blindly, that is, without accurate localization of the lesion. I know that clinical evidence of disease in the brain is as good here in St. Louis as it is anywhere, but one cannot with certainty tell the extent of brain lesions when one depends upon clinical evidence alone. Neither can one obtain such information from ventriculography. I have seen metastatic malignant lesions of the brain in which the ventricular system appears normal. The procedure of ventriculo-encephalography, on the other hand, can demonstrate such lesions.

I have treated metastatic carcinoma of the brain and have obtained good clinical response where it was possible to localize accurately the lesions and employ small fields of irradiation.

The neurosurgeon in many instances has the wrong conception of what good roentgen therapy entails. As a matter of fact, it is the lack of good localization of the site and extent of brain tumors and adequate roentgen therapy thereafter that has accounted for the wide difference of opinion concerning the value of irradiation.

One does not have to treat all brain tumors in university hospitals. There are many radiologists who can administer the radiation as well as one can in university hospitals, provided the necessary information is supplied to them. Such information includes accurate localization and size of portals, isodose curves and dosage.

There are some of Dr. Furlow's colleagues (neurosurgeons) who are enthusiastic about irradiation in the treatment of brain tumors. I am sure that if others would utilize procedures, such as we have described, before irradiation, the results obtained would provide better information for evaluation of the effectiveness of roentgen therapy.

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TWO MILLION VOLT ROENTGEN THERAPY USING ROTATION*

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INTRODUCTION

ROENTGEN rays produced at 2 million volts are fully equivalent in their distribution of spectral energy to the gamma rays emitted by radium in equilibrium with its products. This quality equivalence with gamma rays establishes the physical basis by which, with the 2 million volt radiation, the rich accumulation of biologic and clinical experience with radium may be utilized directly, and assures for such supervoltage radiation those attractive properties of penetration, freedom from scatter, and increased skin and bone tissue tolerance which have long been enjoyed by radium therapists.

To this quality equivalence with radium gamma radiation must be added the advantage of relatively unlimited quantity. The intensity in the beam of the 2 million volt source, such as the Van de Graaff accelerator used in this studies, is somewhat greater than the output of 5,000 gm. of radium—or more than twice the total available world supply. This quantity of 2 million volt radiation permits the use of superior techniques of dosage administration, including adequate filtration and treatment with the patients at long distances from the source.[9] Such advantages have always been denied by the low intensity of radium-beam sources and have been only partially attained by the less penetrating radiation produced with roentgen therapy equipment.

Moreover, this gamma-equivalent radiation of high intensity proceeds from a small spot source and with such an angular distribution that uniform illumination of small and large fields can readily be obtained with sharply defined field edges. The 2 million volt roentgen radiation proceeds through tissue as a directed beam relatively free from scatter, with little energy absorption in adjacent tissue. These favorable physical properties inherent to the use of higher voltages bring closer the prospect of irradiating deep tumors with adequate and uniform doses and with minimal damage to skin and intervening tissue. Optimal irradiation of deep tumors is achieved when physically and biologically superior radiation is combined with the best techniques of administration. It is the purpose in this paper to report on studies made at the Massachusetts Institute of Technology on the irradiation of typical sites of deep tumors with 2 million volt roentgen rays using a rotational technique involving the continuous rotation of the patient about an axis through the tumor.

CHARACTERISTICS OF 2 MILLION VOLT RADIATION

The roentgen rays used in these studies were produced at 2 million volt constant potential by an electrostatic accelerator of the Van de Graaff type insulated in compressed gas at 27 atmospheres pressure. This radiation source was engineered and

* Presented at the Thirty-second Annual Meeting, American Radium Society, New York, N. Y., May 25–26, 1950.

produced by the High Voltage Engineering Corporation from experimental units developed at the Massachusetts Institute of Technology. The voltage source and tube

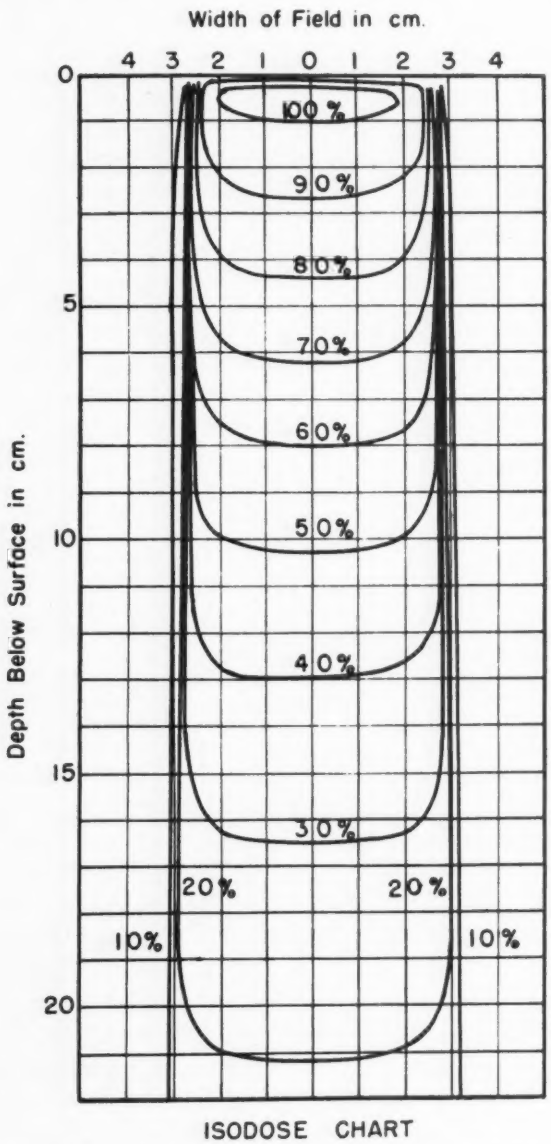

Fig. 1. Isodose chart of 2 million volt roentgen-ray beam of 5 by 5 cm. width, traversing tissue from 100 cm. distance; 6.8 mm. of lead equivalent filtration.

are contained within a steel pressure chamber 30 inches in inside diameter and 65 inches long. The target end of the roentgen-ray tube extends 6 inches beyond the base of the tank and is surrounded by such a thickness of lead that the radiation is attenuated to safe proportions except in the direction of the useful beam. The roentgen-ray beam is diaphragmed by two sets of lead sliders 2 inches thick which define a rectangular aperture adjustable from

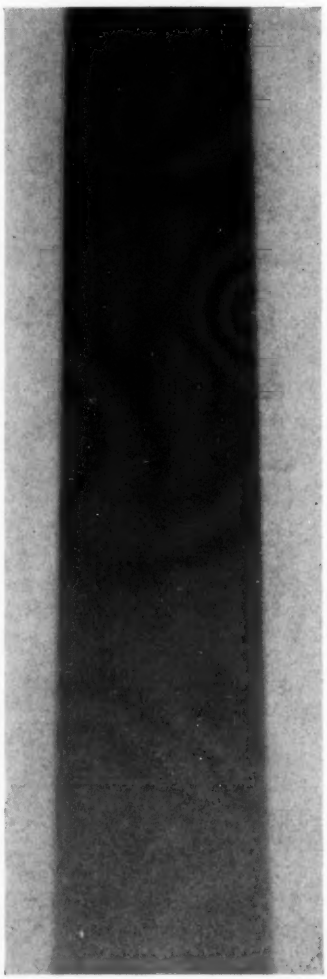

Fig. 2. Photographic film sandwiched between masonite and exposed to 2 million volt roentgen-ray beam of 5 cm. width at 100 cm. distance.

complete closure to a field dimension of 30 cm. at a distance of 100 cm. Additional round diaphragms and shapes for special fields may readily be introduced by attachment to the portal end of the lead enclosure. A visible light beam which coincides in position with the roentgen-ray beam is provided to facilitate the adjust-

ment of the patient for treatment. A dosimeter thimble is also provided in the path of the roentgen-ray beam, the integrated dose at the axis of rotation being indicated continuously at the control panel. The roentgen-ray output of the Van de Graaff accelerator operating at 2 million volts and 250 microamperes is 75 r per minute measured at 100 cm. distance with 4 mm. of air-equivalent wall materials on the thimble and with an equivalent of 6.8 mm. of lead filtration. The half-value layer of this radiation is 12.5 mm. of copper.

Figures 1 and 2 show the distribution of ionization in depth of tissue produced by a 2 million volt roentgen-ray beam of 5 cm. width. The outstanding characteristics of such radiation include the increased depth dose at 10 cm. and beyond, the clean demarcation of the defined beam and its relative freedom from scattering, and the low ionization density in the first few millimeters of tissue at the portal of entry. This skin-protecting effect, which arises because of the several millimeters of tissue thickness required to build up maximal ionization density, accounts for the marked increase in the threshold erythema dose (TED) and skin tolerance of supervoltage rays. In previous studies[8] it has been observed that the threshold erythema dose is reached when about 4,000 tissue r has been passed through the skin in 300 r daily doses. By both Strandqvist's[7] and MacComb and Quimby's[4] methods of reducing fractionated doses, this is equivalent to a single dose threshold erythema dose of about 1,700 tissue r.

An important advantage of supervoltage rays lies in the diminished volume dose in gram-roentgens absorbed by the patient as a result of the delivery of a given deep tumor dose. Comparative studies as yet unreported have shown that with 200 kv. radiation, over 50 per cent more energy in ergs must be absorbed by the patient than with 2 million volt roentgen rays in order to deliver the same dosage to the 10 cm. depth with a 10 by 10 cm. field. Moreover, the larger volume dose required with 200 kv. radiation is concentrated entirely in the tissue intervening between the surface and the tumor site. The relatively low volume dose engendered with 2 million volt roentgen rays and its more favorable distribution in the irradiation of a deep tumor should go far toward accounting for the lower incidence of nausea and other systemic reactions and the reduced permanent damage to normal tissue than with roentgen treatment previously employed. More important, the favorable distribution of supervoltage radiation is a factor in the attainment of the adequately high doses to the tumor-bearing region required for successful clinical results.

ROTATIONAL AND MULTIPORTAL THERAPY

The possibility of significantly improving the delivery of adequate and uniform deep tumor doses is realized when the superior penetrating and skin-favoring characteristics of 2 million volt radiation are combined with effective cross-firing techniques. Rotation of the patient about an axis passing through the tumor with the projected tumor area continuously illuminated by the beam represents the limit to which multiportal cross-firing can be carried out in a single plane. That the rotational technique, advocated at various times for more than forty years, has so far received only exceedingly limited application may be due to the impression that its clinical use is difficult and to the unavailability in the past of sufficiently penetrating radiation to irradiate deep tumors effectively through the thicker body sections. This latter quality factor is an important, but not a determining limitation, as shown by the noteworthy work of Nielsen[5] and his associates in Copenhagen in the rotational therapy of the esophagus with 180 kv. roentgen rays.

An outcome of the studies which are reported herein is a quantitative appraisal of the advantages which can be obtained with rotational therapy and the realization that its clinical use is actually far more practical and accurate than has been generally ap-

Fig. 3. Target end of 2 million volt Van de Graaff generator is shown directed toward masonite phantom used in dose distribution studies of pelvic cavity. Phantom is mounted on rotation stand.

preciated. It has become evident that rotational therapy, when combined with sufficiently penetrating radiation, is often easier to execute than conventional multiportal therapy and is applicable to a wide variety of tumor sites and sizes. This combined therapy technique has been found to produce a substantially uniform dose distribution through the selected tumor volume with greatly reduced damage to surrounding normal tissue. These factors in turn permit the delivery of more adequate doses to the tumor and the more complete inclusion of potentially tumor-bearing tissue in the field than with other methods. It has also become clear that, in general, rotation of the patient, sitting or standing, about a vertical axis is usually superior to radiation with the patient in the supine positions which have often been preferred in the past.

STUDIES ON DOSE DISTRIBUTION ON PHANTOMS

The clinical use of 2 million volt radiation was preceded by physical studies on dosage distribution in which both rotational and multiportal techniques were applied to phantoms. Figure 3 shows the beam-defining target end of the Van de Graaff accelerator directed toward a masonite roentgen-ray phantom which closely simulates the shape, bone structure and absorption characteristics of the human abdominal section. The dosage distribution is recorded as variations in photographic density on a film which has been compressed between sections of the phantom and which lies in the plane of irradiation. The density distribution of the developed film is converted photometrically into relative roentgen-ray dose curves by using a calibration obtained from a separate film strip on which a wide range of densities were produced by known doses. Photographic studies made with 2 million volt radiation* yield more detailed in-

* In the energy range from 1.5 to several million volts, photographic studies are fortunately far less subject to experimental difficulties than for either far higher or lower energies. Contrary to film studies with 200 kv., at 2 million volts the photographic density is virtually independent of atomic number of the absorber constituents, and is not affected by air gaps between film and phantom, nor by the paper cassette. Type A Eastman screen film with black paper cassette and conventional developer techniques were used in most of these studies.

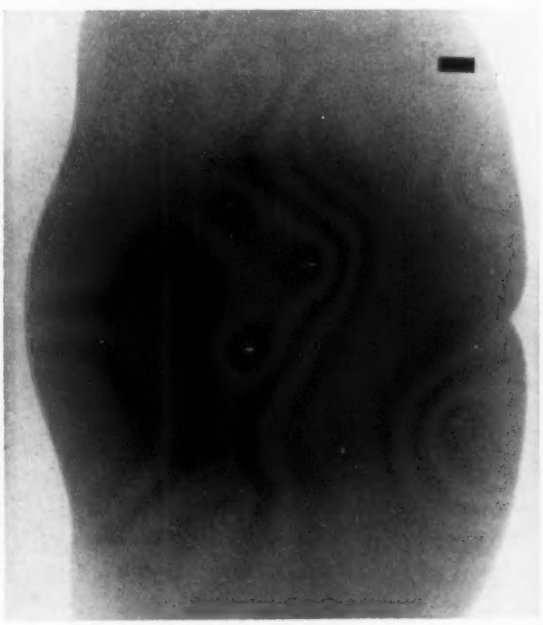

Fig. 4. Photographic film sandwiched in pelvic section of phantom and irradiated by 15 cm. circular beam of 2 million volt roentgen rays during rotation.

formation than ionization chamber measurements and, when properly employed, can quickly produce a quantitatively accurate picture of dose distribution.

The film shown in Figure 4 represents the dosage distribution resulting from the irradiation with 2 million volt roentgen rays of the pelvic cavity during rotation with a 15 cm. diameter field at 108 cm. target-to-axis distance (TAD). This is accomplished with patient or phantom vertical and with the roentgen-ray beam in the horizontal plane. This rotational therapy technique might be indicated in advanced stages of cancer of the cervix or other tumors involving regions well dispersed within the pelvic cavity. The result of rotational therapy with a circular field is to illuminate continuously a spherical region of corresponding diameter which can be centered inside the bony pelvic structure. The roentgen-ray dose falls off markedly with each centimeter removal from the illuminated region because of the fractional time that these outlying regions are exposed.

Figure 5 shows the corresponding isodose study of the rotational treatment of the pelvic cavity and indicates the extent to which the dose sustained in the joints, anterior portion of the bladder, posterior portion of the rectum and skin lies below the tumor dose.

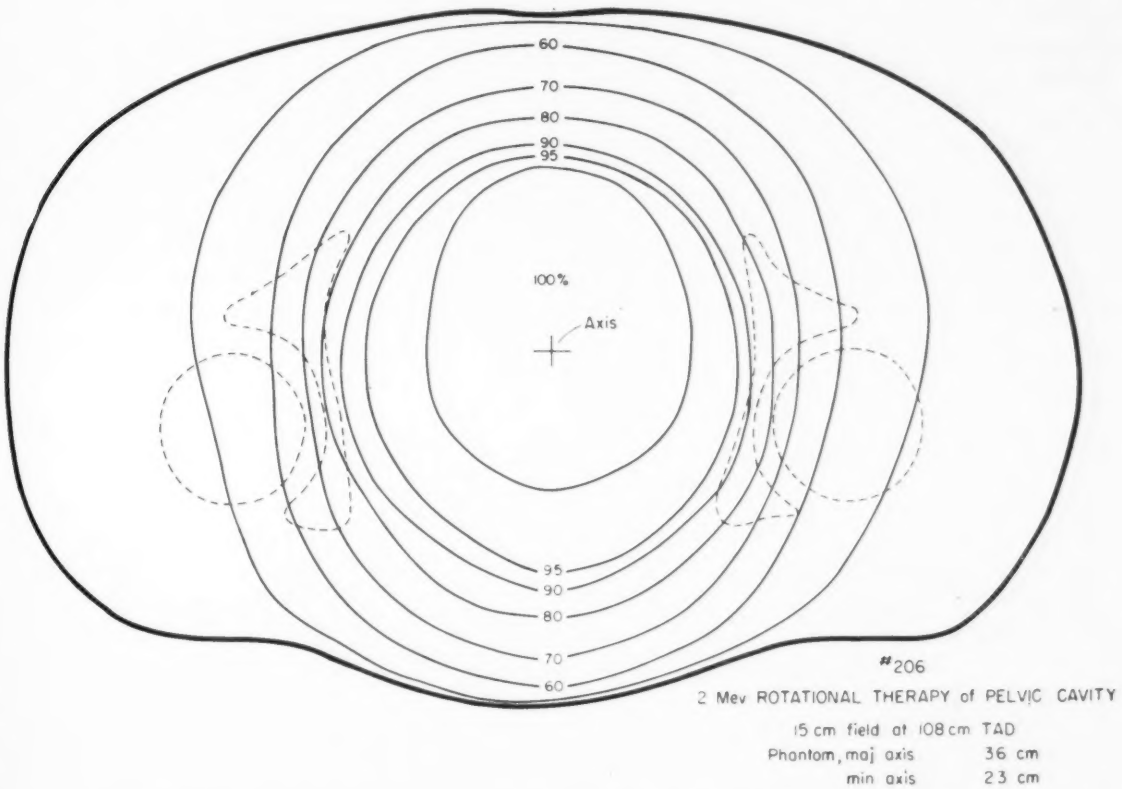

Fig. 5. Isodose chart of rotational treatment of pelvic cavity using 2 million volt radiation, 15 cm. diameter field, 108 cm. target-to-axis distance.

Figure 6 represents the isodose distribution obtained in the irradiation of the pelvic cavity when protection of the bladder and rectum had been secured through the use of lead absorbers both anterior and posterior to the patient. In clinical treatment to date, efforts at protection have been directed toward trimming the circular field to reduce the dose sustained at the joints

and rectum. As discussed below, it has been found possible to reduce irradiation of the lower bowel by applying a tight binding to the abdominal section while the patient is in the Trendelenburg position. Similar rotational procedures with smaller circular fields are used in treating cancer of the

the roentgen-ray beam essentially horizontal and directed at the tumor region. This is illustrated in Figure 8 in which the patient is shown in position for treatment of the pituitary. Essentially similar positioning is used in the treatment of nasopharyngeal tumors, lymph nodes in the

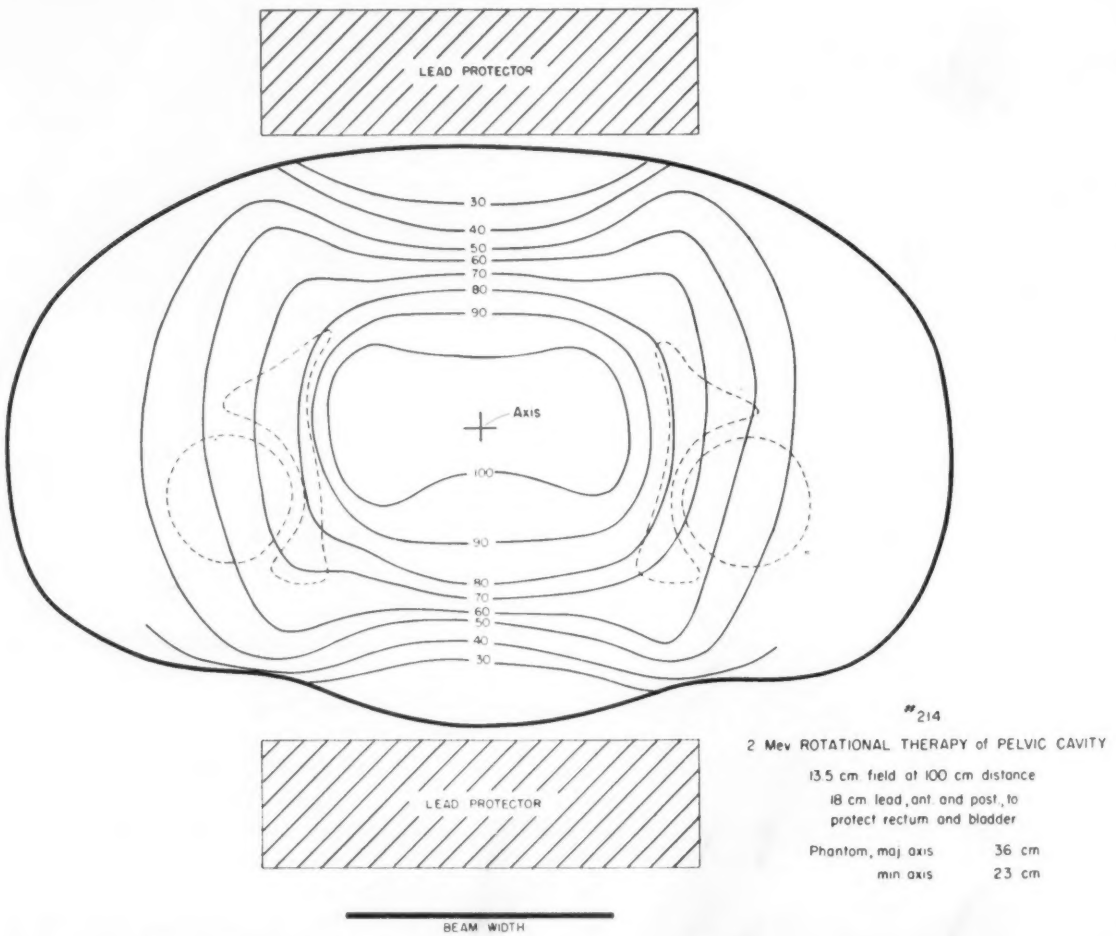

Fig. 6. Isodose chart of rotational treatment of pelvic cavity with absorbers to reduce dose in bladder and rectum; 2 million volt radiation, 13.5 cm. diameter field, 110 cm. target-to-axis distance.

bladder. Figure 7 shows the dose distribution obtained in the rotational treatment of the pituitary with a field 5 cm. in diameter.

PROCEDURE FOR ROTATIONAL THERAPY

The most useful arrangement for rotational therapy has been found to be with a vertical axis of rotation passing through the tumor, the patient standing or sitting, with

neck, and tumors of the tonsil, larynx, thyroid and esophagus.

Firm support of the patient is provided by a single vertical steel bar to which supports of the head, arm, chest, abdominal section and thighs, as well as chair seat, can be attached as required. This steel member is lined up with the axis of the beam for less than 2 per cent of the time of irradiation and provides a small measure

of protection to the spinal column and cord. The support under the arm and particularly the firm juxtaposition of the spine to the supporting bar are essential to the maintenance of the patient's position during treatment.

The principle of rotational therapy requires in general that the axis of rotation coincide with the axis of the tumor being irradiated. This is accomplished by shifting the patient on the rotating stand until coincidence is established between the tumor and rotation axis. For this purpose two steel traverses which move at 90 degrees to each other are mounted above the rotating element. The patient is first placed in the anteroposterior position facing the roentgen-ray source. The generator is elevated to the desired height and angle by the motorized controls. With the aid of a visible light beam which coincides in position with the roentgen-ray beam, the size of the field is adjusted to cover the required tumor area. Special lead applicators have been acquired to facilitate the definition of field shapes which are other than rectangular or circular. The positioning of the field is first determined by making use of the available knowledge of the size and location of the tumor and by checking with reference points in the skeletal structure. When a satisfactory anteroposterior location has been achieved, the stand is rotated through 90 degrees for a corresponding lateral adjustment. Occasionally this process is repeated until satisfactory irradiation of the tumor is believed to have been achieved by the selected field size and shape and orientation of the patient. The success of this positioning is then confirmed by taking a roentgenogram with 2 million volt radiation in both the anteroposterior and lateral positions. These films are first exposed with the selected field and then with an enlarged field so as to produce a superimposed exposure. It is interesting that 2 million volt radiation has considerable diagnostic value with this procedure. Primarily because of the greatly reduced scattering, the developed film shows the bony structure with adequate detail and is especially useful in delineating air passages. Readability over a wide range of body thicknesses is also secured, as has been reported in supervoltage industrial roentgenography.[2] It has been found that photographic check is required only for the first few treatments and, with experience, is occasionally not needed for certain tumors in easily accessible regions. Determination of the patient's ability to

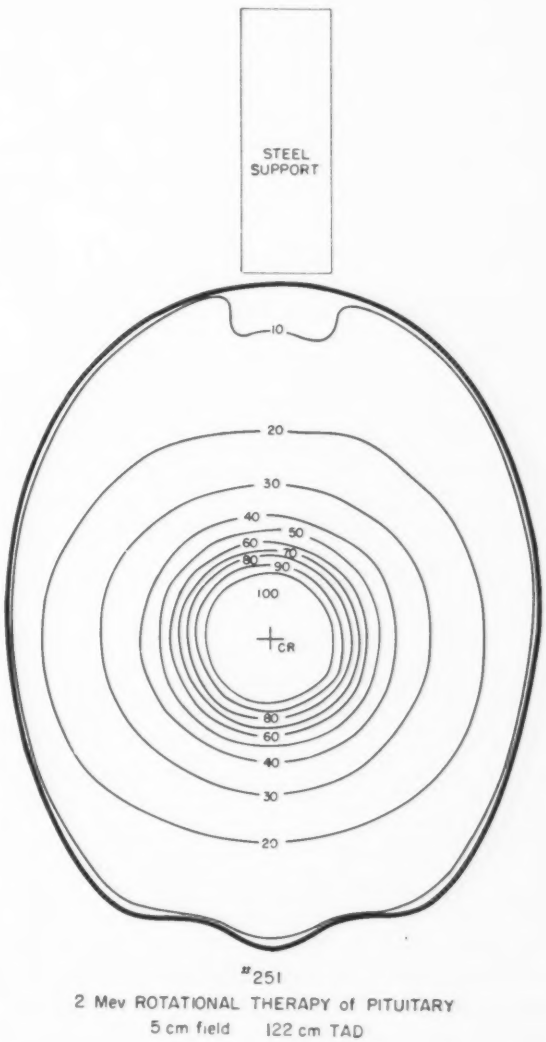

Fig. 7. Isodose chart of rotational treatment of pituitary with 5 cm. diameter beam of 2 million volt roentgen rays. Plane of rotation passes through frontal lobes and below cerebellum. Skin dose is less than 10 per cent of tumor dose and below epilation level.

maintain the position in which he has been placed has indicated that generally he will remain within 4 mm. in the lateral plane and 2 mm. vertically.

When a single rotational field is employed in the treatment of regions in which tissue thickness differs widely, it is possible with both radial and vertical filtration. In this application rotation through only a sector is used, and the field is caused to build up a band of ionization passing through the involved regions, but remaining tangential to the chest wall. It is planned to determine optimal methods of

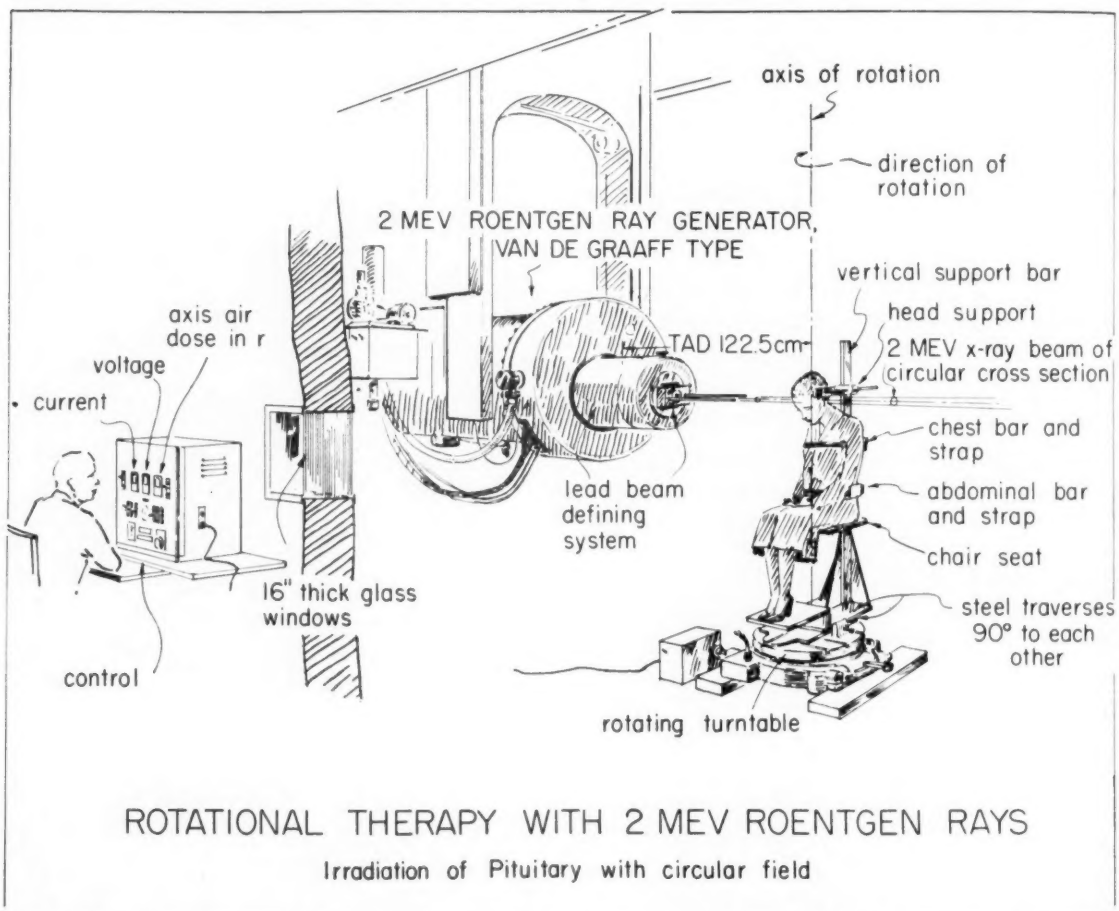

Fig. 8. Rotation mount and 2 million volt roentgen-ray source are shown arranged for treatment of pituitary.

to secure a uniform tumor dose by the use of compensating copper filters. For example, cancer of the thyroid with spread to the supraclavicular and neck regions can be treated with a single rotational field of special shape in which the upper portion of the field is filtered to the appropriately reduced intensity. In the treatment of cancer of the breast, effective irradiation of the breast, sternum, and axillary and supraclavicular regions can be accomplished by a single field of complex shape irradiating typical tumor types and to present the more effective methods and their dose distributions in future publications.

CLINICAL ASPECTS

Two million volt roentgen rays combined with rotational techniques enable the radiologist for the first time to deliver at any desired rate an adequate amount of high quality radiation to any part of the body in the form of a localized but uni-

formly irradiated cylinder or sphere. The success of this new form of therapy must be based to a large extent on the foundation of clinical knowledge acquired by many investigators using radium and conventional roentgen rays over many years.

Careful evaluation of clinical literature led to the selection of 6,000 r as the total tumor dose to be used in the treatment of epidermoid carcinomas in the initial series. This dose of 6,000 r is measured in the tumor tissue and delivered over a period of thirty-five days when extensive tissue regions require irradiation. According to Strandqvist's[7] analysis, this dose corresponds to about 2,200 r delivered in a single massive dose, an amount of ionizing energy generally conceded to be adequate for the cure of skin cancer of the squamous cell type. The work of MacComb and Quimby[4] and of Arneson[1] on the equivalence of divided and massive doses gives further confirmation of the probable adequacy of 6,000 r delivered in this period of time to all involved tissue regions. It will remain, however, for the evidence of time to determine whether or not doses which are clearly sufficient for superficial tumors will also prove adequate in the therapy of more widespread disease.

It is fortunate that radiation which corresponds closely in its physical and biologic characteristics to the gamma rays of radium has nearly optimal properties both in the avoidance of damage to the skin at the portal of entry and in minimizing the effects on bone tissue. Spiers[6] and Wilson[11] have shown the physical basis upon which to expect minimal damage to bone tissue with radiation in the energy range of several million volts and including the gamma rays of radium. In this energy range, fortunately, both the photoelectric absorption and the pair production absorption processes are negligible, the remaining Compton absorption process depending solely on tissue density and not on a high power of the atomic number of the constituent atoms. Nevertheless, in the fifty-three years of radiology it has not yet been possible to determine the ultimate tolerance of normal tissue, especially bone, intestine, kidney, brain and lung. It will be an important part of this effort to contribute as far as possible to more precise information on these points.

It was appreciated that the intestinal tract is most sensitive to radiation and that energy absorption in this region should be minimized whenever possible. This has been accomplished in treating pelvic tumors by strapping the small intestine out of the pelvis with the patient in the Trendelenburg position, using a large 6 inch ace bandage. After the patient is wrapped tightly in such a way as to keep the intestinal regions above the field of irradiation, he walks to the rotational stand and is placed in position for therapy. In cases in which the rectum is not involved by tumor, a protective shield has been devised which considerably reduces the dose sustained by its posterior wall. In a corresponding way it has been found possible to provide special protection for other sensitive regions when necessary. When lymph nodes are involved at the time treatment is instituted, an effort is made to include the entire lymph drainage area in the field of irradiation.

TREATMENT

The following program of treatment has been in progress since November, 1949, a total of 60 patients having received treatment in the period up to May 20, 1950. In all cases 2 million volt constant potential radiation with a half-value layer in copper close to 13 mm. was used. The target-to-axis distance was maintained at 123 cm. and fields were devised to cover the known tumor sites and the regions of potential spread as far as possible.

I. Epidermoid Carcinoma.
   A. Primary tumors are given 6,000 r in thirty-five treatment days at 170 r daily. For lesions requiring portals under 5 cm., the 6,000 r is delivered in thirty treatment days or less.
   B. Metastatic tumors are given 6,600 r in forty treatment days. All patients

Fig. 9. Pituitary adenoma. One month after treatment with 4,000 r in seventeen days, showing no skin reaction or epilation.

with lesions of this type which may be secondarily infected are given antibiotics prior to and during therapy.

II. Carcinoma of the Thyroid.
Primary and secondary carcinomas are given 4,800 r in twenty-eight treatment days at 170 r daily.

III. Carcinoma of the Breast.
6,000 r in thirty-five treatment days at 170 r daily to breast, axilla on affected side, infraclavicular and supraclavicular regions and both internal mammary regions.

IV. Carcinoma of Ovary (localized to pelvis).
6,000 r in thirty-five treatment days, using a sphere no larger than 15 cm. in diameter.

V. Lymphoid Tumors (local or regional and considered unicentric in origin).
2,400 to 3,000 r in fifteen treatment days, with large enough portals to include all surrounding lymphatics.

VI. Testicular Tumors.
Dosage as outlined by Friedman[3] and co-workers, but administered at 170 to 200 r daily. Rotational treatment may avoid some of the complications which he encountered.

VII. Pituitary Adenoma.
4,000 r in seventeen to twenty treatment days, using a spherical portal 3 to 5 cm. in size.

VIII. Brain Tumor.
A. Gliomas, fibrillary astrocytomas, oligodendrogliomas, glioblastoma multiforme, meningeal sarcomas—7,500 r in forty-four treatment days.
B. Medulloblastomas and treatment of entire cerebrospinal fluid tract 2,400 to 3,000 r in thirty days.
C. Pinealomas—2,400 to 3,000 r in fifteen to twenty treatment days.

IX. Carcinoma of the Gastrointestinal Tract.
With the exception of the epidermoid carcinomas of the esophagus and rectum it is planned not to treat carcinoma primary in the gastrointestinal tract by this method until more experience and knowledge are available.

In the utilization of 2 million volt rotational therapy it has been considered necessary to make careful clinical evaluation before patients are chosen for this type of treatment. Careful blood studies are carried out before, during and subsequent to irradiation. So far, no serious change has been noted in the blood even with 6,000 r delivered to relatively large fields. Decreases in the platelet count and in the white blood cells and total eosinophil count have been consistent, but in no case serious. Liver studies have been made before and after treatment when appropriate. In 3 cases abnormal liver function was found before treatment, in 1 case because of metastatic malignant disease and in the other 2 because of primary liver disease. Serial biopsies are performed weekly in the accessible tumors. In malignant disease of the bladder, lungs and cervix, Papanicolaou smears are being done.

Damage to skin and normal tissue is significantly less with this method (Fig. 7, 8, 9, 10 and 11). It has been possible to administer higher total doses and to include more adequately regions of potential lymphatic spread than with conventional methods. The objective of avoiding wet

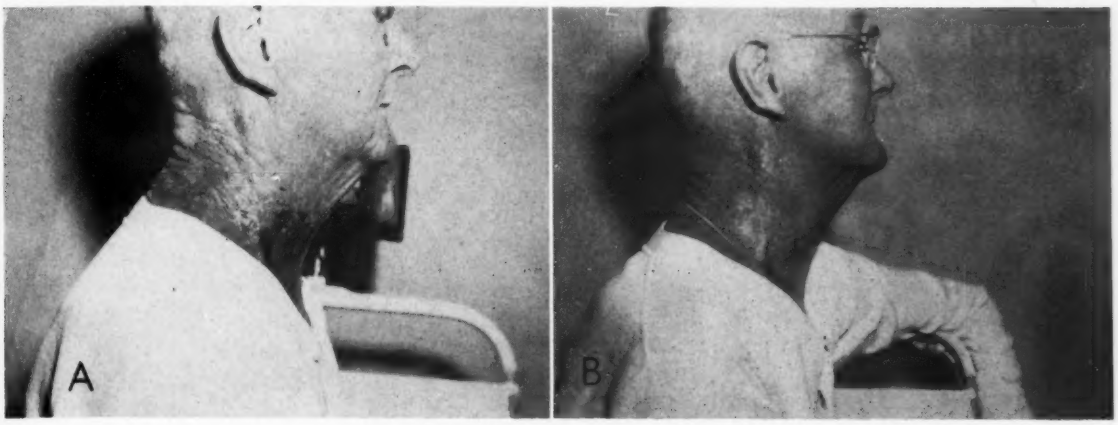

Fig. 10. (*A*) Appearance of patient following treatment with 6,600 r delivered in forty days for epidermoid tumor of postcricoid region with large fixed nodes. (*B*) Seventeen days later.

tissue reactions has been achieved in most instances. The comfort of the patient and the diminished incidence of nausea have been outstanding.

Acknowledgment is made of the generous grant of the American Cancer Society which assisted much of the work reported in this paper, and to the Godfrey M. Hyams Trust whose support to the Massachusetts Institute of Technology through the years has led to the development of the supervoltage roentgen-ray equipment for medical use.

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Fig. 11. Slight reaction can be seen three weeks after treatment with 6,000 r for localized carcinoma of bladder; portal, 9 cm. sphere, 2,000 kv. (c.p.) rotational, 170 r daily.

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THE APPLICATION OF RADIOACTIVE COLLOIDAL GOLD IN THE TREATMENT OF PELVIC CANCER*†

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RECENT medical literature includes a voluminous amount of material regarding the treatment of cancer of the cervix uteri. This new surge of concern in the therapy of cervical cancer is perhaps due to the revived interest in the surgical approach to this problem. The proponents of surgical treatment contend that although present day radiological therapeutic technique has developed to extreme efficiency it still falls short in the successful treatment of even all early cases. These failures are readily explained by the anatomical and pathological characteristics of carcinoma of the cervix. Extension of the tumor from its cervical site is almost entirely by direct and lymphatic infiltration laterally along the uterine vessels and Mackenrodt's ligaments. This is accompanied by a high incidence of metastatic tumor in the regional lymph nodes in cases clinically felt to be localized. Therefore, the results of any therapy would be expectantly poor once the tumor has spread beyond the areas accessible to surgical excision or beyond the effective range of irradiation. Any treatment to be considered adequate must of necessity include a wide volume of tissue beyond the uterus itself. Despite the inadequacies of irradiation, surgery still fails to exceed irradiation results on a statistical basis, when similar material is compared and seemingly for the same reason. From an analysis of failures from both techniques, the majority of recurrences are found in the pelvis, both in lymph nodes and in cellular tissues lateral to the uterus. Since these failures can only be explained on the basis of residual cancer in inaccessible areas after completion of the treatment, it is only logical to expect further advancement in the treatment of this disease to depend on the development of better methods which will direct themselves toward the destruction of residual cancer in the pelvic lymph nodes and, perhaps more important, in the fields of lymphatic drainage.

With these points in mind animal experiments were undertaken employing radioactive colloidal gold in pectin solution as described in a previous paper.[1] From these experiments it was found that transplanted squamous cell carcinoma in mice could be cured safely and completely by the interstitial injection of radioactive colloidal gold. The dosages necessary were also defined. These experiments showed that the gold, when injected into the paracervical tissues of rabbits, entered the lymphatic system and reached the regional lymph nodes. Definite radiation effects were noted in the lymphatics and in the lymph nodes concerned. Tissue tolerance levels by this form of therapy were also studied. Because of these findings we were encouraged to continue with these experiments at a clinical level.

The purpose of this paper is to present the findings of a few clinical experiments that were performed in an attempt to improve the present means of delivering safely and selectively higher amounts of radiation to desired volumes of parametrial tissue.

[1] Sherman, A. I., Nolan, J. F., and Allen, W. M. Experimental application of radioactive colloidal gold in treatment of pelvic cancer. Am. J. Roentgenol. & Rad. Therapy, 1950, *64*, 75–85.

* This work was performed with the aid of a grant from the Atomic Energy Commission, under direction of the Office of Naval Research.

† From the Washington University School of Medicine, Department of Obstetrics and Gynecology, and the Barnes, St. Louis Maternity and Barnard Free Skin and Cancer Hospitals, St. Louis, Missouri. Presented at the Fifty-first Annual Meeting, American Roentgen Ray Society, St. Louis, Mo., Sept. 26–29, 1950.

Radioactive gold was chosen for several reasons. It has a safe half-life of 2.7 days. Its emission spectrum consists of a beta ray of 0.9 million electron volt and a gamma ray of 0.44 million electron volt. This tends to give it an excellent localizing radiation. In addition, it is non-toxic, both chemically and physiologically in the metallic form in which it is used. Also, it is easily irradiated and manipulated into the colloidal form, as used. This form of gold has a purplish color which allows it to be visually traced wherever present.

This report consists of 13 cases. There are 10 cases of carcinoma of the cervix, 1 of carcinoma of the vulva, and 2 of inguinal lymph node metastases. All cases were diagnosed in the Washington University Tumor Clinic, all had biopsy confirmation and were classified according to the League of Nations Classification.

During the preliminary experiments autopsies showed that as much as 50 to 60 cc. of colloidal gold could easily be injected into each parametrium through the vagina. A technique of injection simulating that of the insertion of radium needles into the parametrium was then developed and employed in all cases presented where gold was injected into the parametrium. Following the usual sterile operative precautions, the fornix to be injected was exposed and a No. 22 gauge spinal needle inserted into the paracervical area and carried through the mucosa, Mackenrodt's ligaments and continued laterally angled at 20 to 30 degrees from the midline, to approximate the pelvic wall. Once satisfactorily in position, the stylet was withdrawn and the syringe containing the gold attached. As the needle was slowly withdrawn the gold was injected. Three sites of injection were usually selected in each parametrium. This technique gives a rather uniform dispersion of the gold throughout the area to be treated. The amount of gold injected in these cases was not intended to be of a cancerocidal dose, but of sufficient volume and radioactive strength to be traced and located at surgery. In addition, 3 of the cervical cases described also had gold injected directly into the cervix.

The patients have been carefully observed following the injections but have shown no untoward reactions. Temperatures have remained normal and there have been no genitourinary or gastrointestinal disturbances. Hematological studies have shown no changes. The amount of radioactivity found in the general circulation has been inconsequential. Figure 1 illustrates the total amount of activity in the entire circulating blood stream. At no time was it found to be of any real significance. The highest concentration found in any of the patients treated was 63 microcuries, which represents 0.12 per cent of the total injection. The highest concentration in any one case was found to occur within six hours after the injection. This rapidly disappeared so that at forty-eight hours less than 15 microcuries were to be detected in the entire blood stream. The patients have been able to return to their work the following day and have had no symptomatic complaints relative to the gold treatment. However, 3 of the patients did develop a peculiar purpuric urticarial rash of the erythema multiforme type, which, although generalized, was chiefly confined to the lower extremities. All blood studies at this time revealed no disturbances. The onset of the rash came between seven to nine days following the injection. It was not troublesome and disappeared in forty-eight to seventy-two hours. Although the exact cause of the rash is not known, it is best explained as due to an individual sensitivity to pectin. Of 2 patients treated at the same time with the same stock solution, only 1 developed the rash.

Following is a description of the cases treated to date. It is not the aim of this paper to advocate the form of therapy as outlined in these cases. The procedure of therapy selected was employed so as to learn as much as possible of the use of radioactive gold without depriving the patient of what is considered an adequate, complete, and safe treatment of her disease.

REPORT OF CASES

CASE I. Patient D.G., a forty year old gravida IV, paragravida IV, was admitted to St. Louis City Hospital Tumor Clinic with the complaints of intermenstrual bleeding and bloody vaginal discharge for six months. The cervix was replaced by an everting granular lesion which bled easily on palpation. Infection was not marked. Fornices were clear and rectal examination revealed no evidence of involvement with tumor. Biopsy of the cervix revealed squamous cell carcinoma, Broders' Grade 2 and 3 and the patient was classified as League of Nations Stage I.

The patient was treated in the following manner. Two radium implantations were performed eight days apart. Each implantation delivered 1,800 milligram hours in a tandem in the uterus and 600 milligram hours to each fornix in a colpostat. The patient thus received 6,000 milligram hours total. No roentgen therapy was administered.

Twenty days after the second radium implantation the patient received 7.5 millicuries of radioactive gold in 7.5 milliliters of solution in each parametrium after the procedure described previously. Three sites of injection were selected in each parametrium.

After twenty-four days' interim, a complete abdominal hysterectomy and lymph node dissection was carried out. Marked fibrosis was present in the lower third of the broad ligaments, in and around lymph nodes, along the iliac, hypogastric and obturator vessels, and in lymph nodes lying around the ureter. Marked fibrosis was found along the ureter just proximal to where it entered the bladder. Black discoloration was noted out in the obturator fossa. Where the discoloration was noted, more induration and friability of tissue was seen.

CASE II. Patient D.F., a forty-two year old gravida 0, was admitted to the Washington University Tumor Clinic with the following pelvic findings: a solitary polyp was found at the external os of the cervix. The cervix around the polyp was injected, eroded and slightly granular to palpation. No evidence of parametrial involvement with tumor was found. Biopsy of the polyp and cervix revealed squamous cell carcinoma of the cervix, Broders' Grade 1 and 2. The patient was classified as League of Nations Stage I.

This patient did not receive radium. Using the technique previously described, the patient received 15 millicuries of radioactive gold in 15 milliliters of solution in each parametrium. Three sites of injection were selected in each parametrium. A complete abdominal hysterectomy and lymph node dissection was done twenty-five days after the above treatment. Black discoloration in the left parametrium,

FIGURE I
RADIOACTIVITY IN BLOOD SUBSEQUENT TO INTRAPARAMETRIAL INJECTION OF Au^{198}

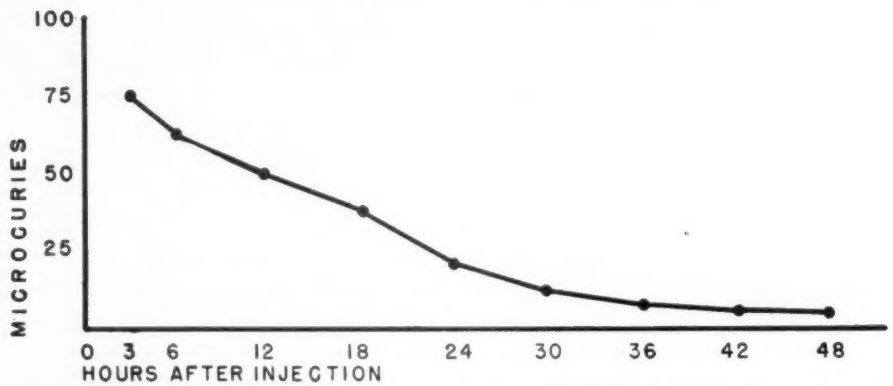

FIG. 1. Graph showing the total radioactivity that enters the entire circulating blood stream.

extending laterally to the pelvic wall, was seen. Discoloration was also present anteriorly over the bladder and between the bladder and cervix. In the right parametrium the discoloration extended somewhat higher up over the brim of the pelvis. No areas of necrosis were demonstrated. It was noted that the parametrial tissues were more friable than usual where gold was present. The hysterectomy was performed uneventfully and lymph nodes along the iliac, hypogastric and obturator vessels were dissected out. Increased amounts of black discoloration were noted in the right obturator space. This area was moderately indurated on palpation. The left obturator space contained a lesser amount but was discolored to some degree. Moderate discoloration was seen around the ureters. No gross evidence of irradiation damage to the ureter could be demonstrated. The patient tolerated the operation without difficulty.

Case III. Patient B.W., a thirty-nine year old gravida III, paragravida III, was admitted to the Washington University Tumor Clinic with the following pelvic findings: the cervix was hypertrophied but well epithelialized except for a 1 cm. area around the external os. The fornices were clear. No evidence of involvement of the parametria with tumor was found.

Biopsy of the cervix presented the typical epithelial changes of squamous cell carcinoma of the cervix, Broders' Grade 1 and 2. The patient was classified as League of Nations Stage I.

No radium was applied to the cervix. Using the usual technique, the patient was treated with radioactive gold. She received 15 millicuries into each parametrium and 8 millicuries into the cervix. Three sites of injection were used in each parametrium. Four sites were chosen for injection into the cervix.

A complete abdominal hysterectomy and lymph node dissection was carried out uneventfully thirty-five days after injection of the radioactive gold. Many lymph nodes were obtained from along the iliac, hypogastric and obturator vessels. Black discoloration from deposition of gold was found concentrated in the parametrial tissues and in the lymph nodes removed. Black discoloration was noted in the sigmoid mesocolon. It is probable that this area was directly injected with the radioactive material. Here, as well as in other areas where the material was found, erythema and slight induration were noted. No gross necrosis was seen. The cervix presented typical evidence of irradiation reaction immediately around the sites of injection. One centimeter away from the periphery of the area of injection no evidence of irradiation was noted.

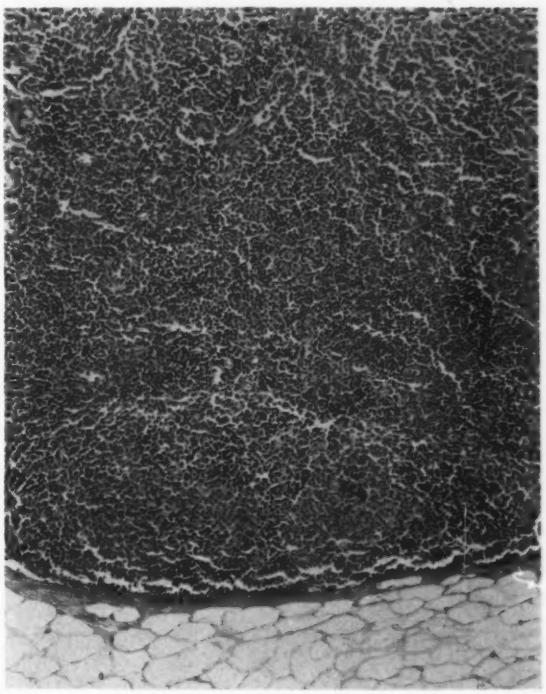

Fig. 2. Photomicrograph of normal pelvic lymph node.

Case IV. Patient V.C., a forty-one year old gravida VII, paragravida VII, was admitted to the Washington University Tumor Clinic with the history of intermenstrual vaginal bleeding, bloody vaginal discharge and backache for twelve months. Pelvic examination revealed an eroded cervix with many small papillary projections into the external os. Fornices were clear. No evidence of involvement of the parametria with tumor was found.

Microscopic examination of biopsies of the cervix revealed squamous cell carcinoma, Broders' Grade 1 and 2. Patient was classified as League of Nations Stage I.

Patient was treated with radioactive gold as follows: 15 millicuries in 15 milliliters of solution were injected into each parametrium with three sites of injection on each side. In addition, the cervix was treated with 20 millicuries

divided into four sites of injection. The patient did not receive radium therapy.

Nineteen days after injection of the gold a complete abdominal hysterectomy and lymph node dissection was performed. The parametria were visibly discolored with gold. Rather marked infiltration of the cul-de-sac and utero-sacral ligaments had obviously taken place. The hysterectomy was uneventful. Many external iliac lymph nodes were obtained as were several hypogastric and obturator lymph nodes. Rather marked discoloration was noted

FIG. 3. Photomicrograph of obturator lymph node after injection of radioactive colloidal gold into parametrium illustrating the radiation effects.

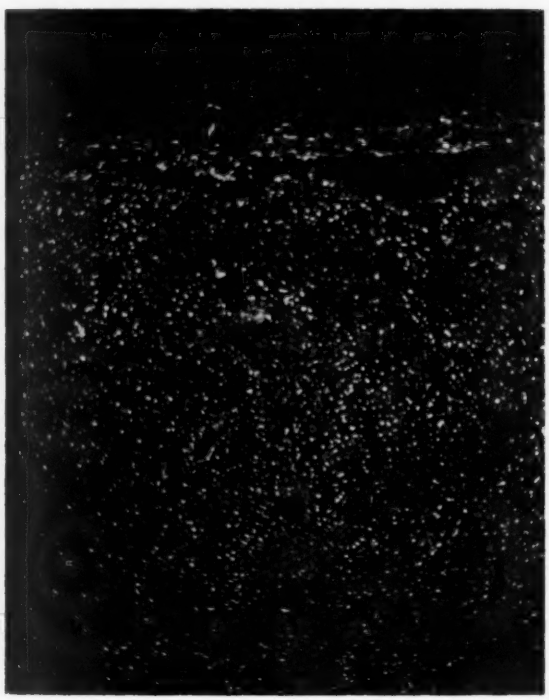

FIG. 4. Dark field exposure of microincineration of same section as in Figure 3. The gold particles show up as bright yellow specks illustrating the distribution of gold particles in the node.

lateral to the ureters and continued out laterally past the obturator nerve into the obturator fossae. Erythema and moderate induration were noted in areas where accompanying concentration of the gold was present. The cervix showed gross evidence of irradiation in the immediate area of injection.

CASE V. Patient N.I., a thirty-eight year old gravida III, paragravida III, was admitted to the Washington University Tumor Clinic with a history of vaginal bleeding and vaginal discharge for six months. Six weeks previous to admission to the clinic, she had had a conization by a private physician which was reported as showing microscopic malignant cells. Examination revealed the external os covered with benign appearing granulation tissue. Minimal induration was present in the cervix. The parametria were clinically free of tumor.

Microscopic examination of cervical biopsies showed squamous cell carcinoma of the cervix, Broders' Grade 1 and 2. Patient was classified as League of Nations Stage I.

No radium was applied to the cervix. Patient was treated with radioactive gold in the following manner: 15 millicuries were administered into each parametrium. Three sites of injection were used on each side. Five millicuries were injected into each site. The cervix was treated with 16 millicuries. Here four sites of injection were selected. The patient was re-hospitalized twenty-eight days after this initial treatment, and a complete abdominal hysterectomy and lymph node dissection was done. Again black discoloration was found in the parametria and along the major vessels in the pelvis. During the lymph node dissection the obturator spaces lateral to the obturator

nerve were noted to contain a rather heavy concentration of gold. The cervix presented typical gross evidence of irradiation damage around the sites of injection of the radioactive material.

Case vi. Patient B.C., a sixty-four year old gravida v, paragravida v, was referred to the Washington University Tumor Clinic from a private physician following a positive cervical biopsy for malignancy. She had had intermittent vaginal bleeding accompanied by increased amounts of vaginal discharge for six months. Examination revealed the cervix to be eroded, hypertrophic and ballooning out laterally and encroaching upon the left lateral fornix. The lesion appeared to be infected and infiltrating. Rectal examination indicated minimal encroachment onto the left parametrial tissues.

Microscopic study of biopsies revealed squamous cell carcinoma of the cervix, Broders' Grade 3 and 4. The patient was classified as League of Nations Stage II.

The patient received 2,000 roentgens (in air) directly to the cervix, delivered by a small transvaginal cone. One week later she received 3,000 milligram hours of radium. In a uterine tandem 1,500 milligram hours were delivered and 1,500 milligram hours in a colpostat. A second implant was carried out one week later with 1,000 milligram hours delivered to the cervix by colpostat and 1,160 milligram hours by uterine tandem. The patient thus received a total of 5,150 milligram hours. The patient was re-admitted twenty-eight days after treatment and given radioactive gold in the following manner: 8 millicuries were injected into each parametrium. The amount was divided evenly between two sites of injection on each side.

A complete abdominal hysterectomy and lymph node dissection was done thirty-five days after injection of the radioactive material. The operation was made more difficult by the presence of marked adhesions. The uterus with a wide block of parametrial tissue on both sides was removed. The lymph node dissection was limited to the nodes along the left major pelvic vessels, where several iliac, hypogastric and obturator lymph nodes were obtained. Discoloration from gold was noted in the left obturator fossa and in the parametria bilaterally.

Case vii. Patient G.A., a thirty-three year old gravida 1, paragravida 0, abortus 1, was admitted to the Washington University Tumor Clinic following a biopsy of the cervix which revealed squamous cell carcinoma of the cervix, Broders' Grade 1 and 2. The patient had been followed in the Gynecological Clinic for five months because of amenorrhea and an acutely "inflamed" cervix. When the cervix did not improve with the usual treatment, biopsies were taken. Pelvic examination revealed the cervix to be eroded over the external os. This area was slightly indurated and granular. No evidence of invasion of the parametria by tumor could be found.

Fig. 5. Photomicrograph of hypogastric lymph node after injection of radioactive colloidal gold into the parametrium illustrating the disruption of the normal lymph node architecture.

Patient was hospitalized and treated with radioactive gold in a manner similar to that previously described. Sixteen millicuries of radioactive gold in 16 milliliters of solution were injected into the right parametrium. Four millicuries were injected at each of four sites. The left parametrium received the same amount of gold particles in inactive form. Here three sites were selected for injection. The cervix was then injected with radioactive gold. Four sites were injected on the anterior, right lateral, posterior and left lateral surfaces of the cervix, 2.5 millicuries being injected at each of

FIG. 6. Photomicrograph of an external iliac lymph node illustrating the distribution of the radiation effects along the subcapsular areas and the reticulo-endothelial pathways.

these areas. The cervix thus received 40 millicuries of active gold.

The patient was re-hospitalized nineteen days after the above treatment, and a complete abdominal hysterectomy and lymph node dissection was performed. At operation the fimbria of the left tube and the ovary were found to be adherent and slightly enlarged to form a mass measuring 4 by 3 by 3 cm. This was found to contain an old unruptured ectopic pregnancy.

Marked discoloration caused by particulate gold was found present in the parametria, along the uterosacral ligaments and around the major blood vessels of the pelvis. Good distribution of the material was found next to the pelvic wall on both sides. Large amounts of gold particles were found present on the anterior surface of the cervix between the cervix and the bladder. Induration and erythema were more noticeable on the right than on the left. Many lymph nodes were removed from the iliac, hypogastric and obturator areas. The patient tolerated the operation well.

CASE VIII. Patient F.R., a thirty-six year old gravida VIII, paragravida VIII, was seen in the clinic with the chief complaint of foul vaginal discharge and irregular vaginal bleeding. Biopsy of a granular eroded area of the cervix showed a squamous cell carcinoma in situ. With the usual technique, 36 millicuries of radioactive gold in 20 milliliters of solution were injected in the right parametrium, while 20 milliliters of inactive gold were injected into the opposite side. The patient was subjected to a radical, complete abdominal hysterectomy and pelvic lymphadenectomy twenty-eight days later. At operation, gold was seen infiltrating the obturator fossae and extending along the lateral pelvic walls to the brim of the pelvis. No areas of radiation damage could be identified even where gold was most heavily concentrated. The injection, operation and convalescence were entirely uneventful.

CASE IX. Patient L.O., a twenty-four year old gravida VI, paragravida VI, was seen in the Tumor Clinic because of profuse vaginal discharge. Biopsy of the cervix, which was enlarged and eroded, confirmed the clinical impression of squamous cell carcinoma. The lesion was classified as League of Nations Stage I.

In a volume of 20 milliliters of pectin solution, 54 millicuries of radioactive gold were injected into the right parametrium, while 20 milliliters of inactive colloidal gold were injected on the left side. This patient received no roentgen or radium therapy. The patient was subjected to a complete abdominal hysterectomy and pelvic lymphadenectomy seventeen days later. At operation gold was seen infiltrating the entire parametria on both sides and extending laterally to the pelvic walls and into the obturator fossae. It also extended up over the sacrum to the promontory of the pelvis. No areas of radiation necrosis were identified although definite radiation effects were noted throughout the right side of the pelvis.

CASE X. Patient J.F., a twenty-four year old gravida III, paragravida II, was seen in the Washington University Clinics because of brownish discharge and contact bleeding during early pregnancy. The patient was two and one-half months pregnant when a biopsy of the cervix was diagnosed as squamous cell carcinoma in situ. Because of the pregnancy and hesitant diagnosis, it was decided not to treat the patient immediately but follow her closely.

However, the patient miscarried one month later. A biopsy following the abortion showed definite invasive carcinoma. The patient received 39 millicuries in 30 milliliters on the right side, and 20 millicuries in 15 milliliters on the left side. In addition, 16 millicuries in 15 milliliters were injected into the cervix. No roentgen or radium treatment was administered. A complete abdominal hysterectomy and pelvic lymphadenectomy was performed thirty days later. The gold showed the usual infiltrative tendencies as described in the previous cases. The patient tolerated the procedure without difficulty.

All the patients have been carefully followed since completion of their treatment. None has shown any persistent tumor or recurrence to the present date and several have been followed for over six months.

On reviewing these cervical cases there is found to be a striking uniformity of results. The parametrial areas, where gold was injected, showed definite radiation effects. Here microscopic examination reveals cellular destruction with accompanying fibrosis. There seems to be a great increase in lymphatics which for the most part are packed full of scavenger cells containing gold particles within their cytoplasm. Throughout the tissues there are many cells of the phagocytic type consisting of large mononuclears, polymorphonuclears and giant cells, all in the process of phagocytosing gold particles. The blood vessels in the areas show the typical radiation effects of endarteritis.

As mentioned in the description of the cases, definite radioactive gold deposits are found in the lymph nodes (Table 1). Definite results of localized radiation are illustrated in these lymph nodes and proportionately more so in those areas which are more heavily infiltrated with gold particles. In these areas one notices a reduction of lymphocytes accompanying cellular and nuclear damage which is manifested by clumping of chromatin, cytoplasmic edema, loss of cell outline, and the presence of debris as a result of nuclear and cytoplasmic disintegration. Lobation of nuclei,

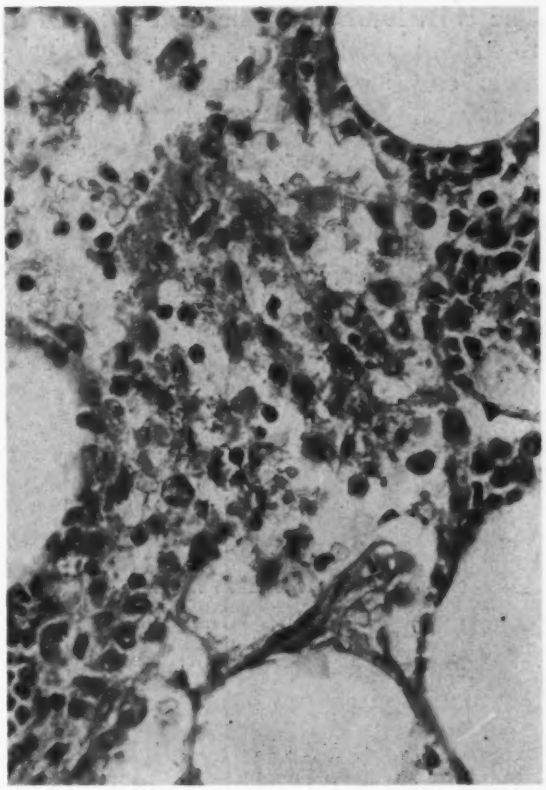

Fig. 7. A higher power photomicrograph showing the gold particles in the phagocytic cells of a lymph node, with resultant adjacent radiation effects.

formation of giant cells and an increased number of phagocytes are evident. There is usually evidence of hemorrhage with large numbers of extravasated red blood cells. Blood vessels are noted to have a peculiar edema of the perivascular connective tissue and some show occlusion due to endarteritis. Some of the lymph nodes removed at a longer interval from the treated time show a sort of healing process consisting of a phenomenon of fibrosis with dense masses of spindle cells. These spindle cells may be the end product of the densely packed cells with pale vesicular nuclei which are seen in the center and the periphery of the lymph follicles in those lymph nodes removed at a shorter interval.

The distribution of these effects is somewhat scattered throughout the lymph nodes, but in some nodes may involve as much as one-half to three-quarters of its volume.

The chief location of the gold is noted in the subcapsular region, the hilus of the node and along the reticulo-endothelial pathways which surround the follicles and seem to cause primarily peripheral shrinking of the follicle with a directly proportional effect to the amount of gold present. In the lymph nodes removed at longer intervals, in which there has been full recovery from the irradiation, the follicular architecture of the node is lost and parametrium, the gold particles were found phagocytosed and contained in the lymphatics. However, the cellular destruction which accompanies the active gold particles was not evident. The nodes contained large accumulations of gold with a resultant macrophagic hyperplasia. This hyperplasia caused a definite decrease in the lymphocytic reticulo-endothelial ratio. However, instead of cellular destruction in these areas, there was an actual increase in

TABLE I

DISTRIBUTION OF RADIOACTIVITY IN THE PARAMETRIUM AND IN THE PELVIC LYMPH NODES

Cases	Parametrium. Per cent of total amount injected	Upper Iliacs. Per cent of parametrial activity	Lower Iliacs. Per cent of parametrial activity	Hypogastric. Per cent of parametrial activity	Obturator. Per cent of parametrial activity	Ureteral. Per cent of parametrial activity
I	0.29	34	17	50	50	
II	0.15	100	100	133	100	
III	0.08	60	20	27	24	25
IV	0.03	33	35	33	66	
V	0.05	100	80	100	100	137
VI	0.35	17	12	20		
VII	0.86	25		50	50	
VIII	0.9	30	80	40	40	

is replaced by a generalized distribution of lymphocytes throughout the entire node. In a few lymph nodes small focal areas of necrosis are found in the region of large accumulations of gold particles.

Although the lymph nodes were carefully scrutinized for metastases, no definite tumor cells were found. However, in 2 of the cases in the parametrium adjacent to the cervix several areas containing masses of atypical cells were seen. These resembled tumor cells but, because of radiation effects in them or in the immediate vicinity, they could not be definitely proved to be of metastatic nature.

As mentioned above, 4 patients had inactive colloidal gold injected on one side while active gold was injected on the opposite side. The inactive colloidal gold, as expected, behaved similar to the active gold. It was picked up by the lymphatic system and carried to the regional lymph nodes. On microscopic examination of the cellular density. Wherever gold was found, instead of finding edema, cytoplasmic destruction and hemorrhage, there was increased cellular activity, marked hyperemia and fibrotic reaction. However, in a very small number of lymph nodes, found just lateral to the ureter where it crosses beneath the uterine artery, a small amount of radioactivity was detected and on microscopic examination showed slight radiation effects. It is believed that this gold must have come from that which was injected into the cervix itself.

Measurements of radioactivity were performed by applying the nodes to a Geiger counter and comparing the activity to that of a known sample of Au^{198}. The activity of the parametrium was determined in a similar manner using a section of the parametrium of approximately the same dimensions as the comparative nodes.

Table 1 illustrates that the gold which is injected into the parametrium is carried to

the lymph nodes where it is accumulated. The concentration in the nodes was found to be 25 to 75 per cent of that left in the parametrium. It is interesting to note that this amount of gold is due to an actual concentration in the node itself, for, on examination of the fat surrounding the node, a definitely smaller amount of activity is found. For example, in patient D.F. (Case II) no increase over background activity could be detected in the fat stripped from the lymph nodes and yet the activity in the nodes was appreciable. In one node counted before and after stripping the fat, the counts increased significantly after the fat was off, illustrating that the fat contained none if any activity and only caused an actual physical barrier to measuring of the radioactivity in the node. In Case III, the activity of two nodes counted separately with the fat stripped off showed 9 and 17 times, respectively, the activity in the node over that in the surrounding fat.

To be sure the concentration of gold in the lymph nodes resulting from the dosages used has not been sufficient to cause entire destruction in the nodes. However, in the animal experiments where the dose was increased to an extremely high amount, many nodes showed complete necrosis. It would therefore be expected that in future experiments where the dose will be increased both in strength and in volume, it will cause a greater concentration in the nodes with a resultant greater effect. This is clinically demonstrated as well by Cases VIII and IX, in which a much larger quantity of activity was used and which microscopically showed a much greater destructive reaction in the lymph nodes and yet fell well within the tolerance level since no unusual damaging effect was found at operation.

The following is a description of the vulvar and inguinal node metastases treated with radioactive gold.

Case XI. Patient E.C., a sixty-one year old gravida V, paragravida IV, was seen in the Washington University Tumor Clinic with a history of vulvar itching and burning for six months, and an ulcerated area on the perineum for four months. Pelvic examination revealed contracture of outlet with the vulvar skin grayish-white and thin. A 0.5 cm. area of ulceration was present on the left labium majus. Several smaller areas of ulceration were present anterior to the urethral meatus and on the fourchette. No inguinal nodes were palpated. A radical vulvectomy was done. Sections revealed leukoplakia of the vulva and squamous cell carcinoma of the vulva.

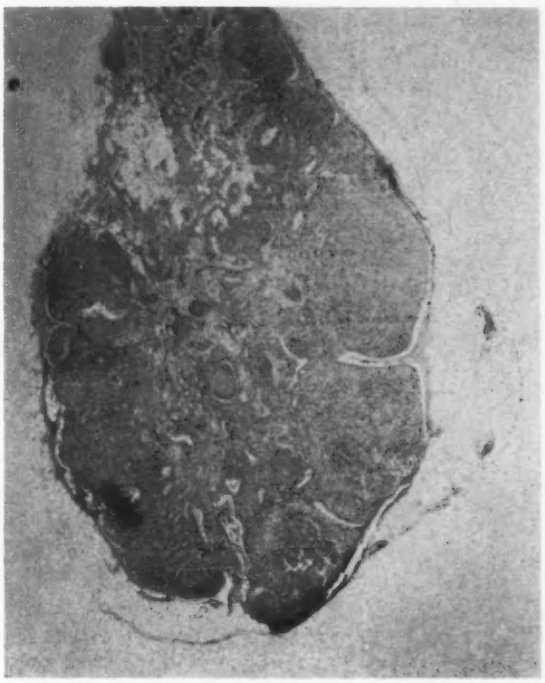

Fig. 8. A low power photomicrograph to show typical over-all appearance of a lymph node irradiated with radioactive gold.

Fifty days later the patient was rehospitalized and radioactive gold was injected into the inguinal areas in the following manner. The abdomen and inguinal areas were prepared and draped. The skin over the inguinal ligaments was injected with 1 per cent novocaine. A No. 22 gauge spinal needle was inserted through the skin overlying the mid portion of the inguinal ligament and directed down along the inferior portion of the inguinal ligament. As the needle was slowly withdrawn, radioactive gold was injected. A similar injection was made along the superior portion of the ligament. The needle was then directed medially and downward until the fascia of the external

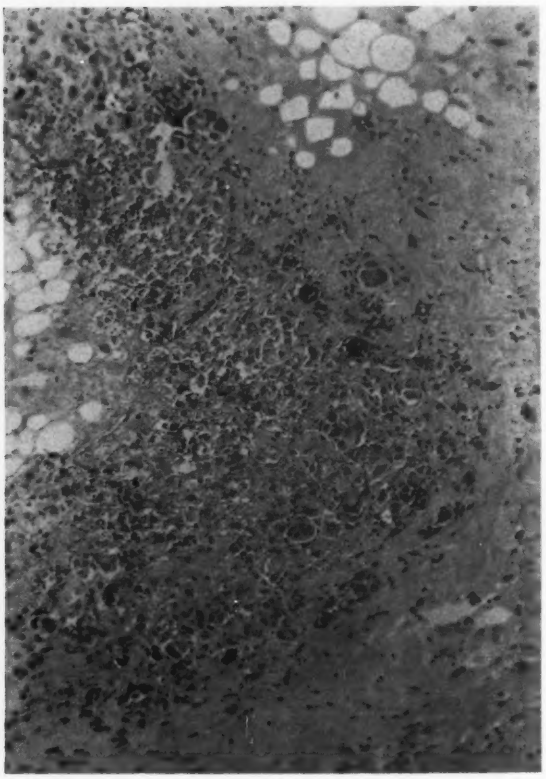

FIG. 9. A photomicrograph illustrating the radiation effects in the parametrium injected with radioactive colloidal gold.

oblique muscle was reached. Here radioactive material was again injected. Injections were then made in a similar manner laterally and downward toward the greater trochanter and inferiorly over the mid portion of the thigh. Two millicuries in 2 milliliters were injected at each point of injection described above. A total of 10 millicuries was injected into each inguinal area with five sites of injection selected on each side.

The patient was again admitted to the hospital fourteen days after the above injection and a radical inguinal lymphadenectomy was performed. The subcutaneous tissues were markedly discolored with particulate gold matter. This discoloration extended down to the fascia of the external oblique muscle and below the inguinal ligament. It was noted that the tissues around the small vessels in the area contained the most marked concentration of the material. A few small areas of liquefaction of the tissues were seen. Lymph nodes removed from the external iliac area contained gross amounts of discoloration. However, this was much less than that seen in the subcutaneous tissues.

Sections of the tissues removed demonstrated particulate gold in lymphatic channels accompanying small blood vessels through the subcutaneous structures. Marked amounts were present in cells of the reticulo-endothelial system. These cells were found in the connective tissue around fat lobules. Uninuclear and multinuclear giant cells, with their cytoplasm darkly stippled with gold particles, were noted. Where the concentration was more marked, edema, hemorrhage and infiltration with polymorphonuclear leukocytes and round cells were very pronounced. Increased amounts of fibrin in the areas were present.

Examination of the lymph nodes revealed moderate amounts of particulate gold present along the periphery and in the reticulum. Definite irradiation effects were present, exemplified by hemorrhage, swelling of cytoplasm and pyknosis of nuclei. No metastatic malignant cells were found in these lymph nodes.

CASE XII. Patient E.W., a fifty-six year old gravida 1, abortus 1, was seen in the Washington University Tumor Clinic in 1946 because of vaginal bleeding for nine months. Examination at that time revealed a firm, non-tender vascular mass measuring 2 by 1 cm., extending downward into the vaginal vault from beneath the urethra. The mass was fixed to the underlying tissue and extended to both labia minora and to the base of the clitoris. No invasion of the vagina beyond the introitus was noted. Biopsies of the tumor mass revealed malignant squamous epithelium. The patient was treated with contact roentgen therapy, 1,000 roentgens (in air) per treatment for seven doses. She then received 1,900 milligram hours in radium needles in and around the tumor mass. Three months later local excision of the urethral tumor was done. The patient was then lost for a period of four years, after which she returned to the Tumor Clinic in answer to a follow-up survey. Since the operation four years previously, the patient had been incontinent of urine. In addition, she had noticed an inguinal mass for six months which had been slowly progressing in size. Examination revealed a 2 by 2 by 1 cm. soft, fluctuant mass lying directly beneath the symphysis. A mass measuring 3 by 3 by 2 cm. was also present in the left inguinal region. The lower margin of the mass was ad-

herent to the inguinal ligament. The patient was treated with radioactive gold. The abdomen and inguinal regions were prepared and draped. The skin over the vaginal and inguinal nodules was infiltrated with 1 per cent novocaine. The vulvar mass was infiltrated with 4 millicuries of radioactive gold in 4 milliliters of solution. Here six sites of injection were selected. The tissues along the inguinal ligament were then infiltrated with 10 milliliters of solution containing 10 millicuries of radioactive gold. The inguinal tumor mass was injected with 15 millicuries in 15 milliliters of solution. The tissues about the tumor mass were injected evenly through ten sites of injection.

A partial vulvectomy and dissection of the femoral, inguinal and external iliac lymph nodes was performed forty-seven days later. Discoloration from deposition of particulate gold was pronounced in lymph channels accompanying blood vessels in the inguinal area. Many femoral, iliac and inguinal lymph nodes were removed and these presented gross evidence of gold discoloration. Marked discoloration was still present in the supportive connective structures of the subcutaneous tissues.

Examination of the vulvar tissues removed demonstrated marked amounts of gold present around the periphery of the 2 cm. diameter mass. Where the particulate matter was concentrated, hemorrhage, edema and many plasma cells were found. Swelling of cell membrane, cytoplasmic edema, pyknosis, karyolysis and karyorrhexis of tumor cells present in the area were noted. No gold had apparently been injected into the center of the mass.

The inguinal masses demonstrated many areas totally destroyed by irradiation. Gold particles were noted along the periphery of tumor masses. The lymphatic channels entering the tumor mass contained many particles of gold. Thus it is shown that these particles did enter the tumor mass through lymphatic channels. Particulate matter was present in the femoral, iliac and inguinal nodes. The irradiation effects described above were similarly found in femoral lymph nodes where gold was present.

Case xiii. Patient A.F., a seventy-three year old female, was admitted to Barnes Hospital as a private patient with the history of having had a partial vulvectomy and right inguinal node dissection six months previously. Examination revealed a well healed right vulvar and right inguinal incisional scar. The left labium majum was indurated, slightly tender and a 1 cm. mass was palpated just below the symphysis pubis. A hard, indurated, nontender mass, measuring 5 by 4 by 2 cm. was present in the left inguinal area. The medial aspect of the mass was in approximation with the left anterior ramus of the pubic bone. The inferior margin rested upon the inguinal ligament. Several smaller shot-like masses were palpated along the course of the inguinal ligament. Microscopic examination of tissue removed at the initial operation revealed malignant squamous epithelium. The patient was treated with radioactive gold in the following manner. The abdomen and inguinal regions were prepared and draped. The skin over the left inguinal region was infiltrated with 1 per cent novocaine. A No. 22 gauge spinal needle was inserted along the inguinal ligament adjacent to the large, previously described mass. As the needle was slowly withdrawn, 6 millicuries were infiltrated around the mass. Other sites of insertion were selected along the inguinal ligament. Here the needle was directed medially toward the midline and deep into the abdominal wall to the fascia of the external oblique muscle. Thus a total of 20 millicuries was administered to the left inguinal masses through four sites of injection. A radical, left vulvectomy and left inguinal node dissection was carried out fifteen days after the above treatment. Subcutaneous tissues around the areas of injection were markedly discolored with particulate gold. This discoloration extended down to the fascia of the external oblique muscle. A large block of tissue was removed from the inguinal area, including the inguinal mass described above and tissue around the femoral vein. Lymph nodes from around the external iliac vessels were removed by dissection. Discoloration of lymph channels accompanying vessels entering the tumor mass could be seen. Gross examination of the lymph nodes revealed gold discoloration. This discoloration was less marked, however, than that seen in the channels in the subcutaneous tissues.

Examination of tissue demonstrated gold particles in and around the periphery of tumor

masses. Particulate matter entering the masses through afferent lymphatic channels was noted. In the immediate area where gold was present, hemorrhage, edema and infiltration with round cells were also found. Swelling of cell membranes, edema of the cytoplasm, pyknosis, karyolysis and karyorrhexis of tumor cells was found.

Gold particles were present in the inguinal, femoral and iliac lymph nodes. Typical irradiation effects were also noted here. The presence of the material in the iliac nodes demonstrated the ability of the lymphatic channels to carry the foreign material to nodes distant from the site of injection.

These cases gave us an opportunity to observe clinically the actual dispersion of the gold. Although the gold was injected at least 3 to 4 cm. beneath the skin surface and was not observed immediately following the injection, twelve to eighteen hours later the gold was diffusely distributed over the entire skin surface. It also gave us an index of activity in the area, for although no evidence of damage was noted in the skin, there was a slight erythematous reaction, and depilation did occur confined to the discolored area. In addition, as described, the gold was found phagocytosed and carried to the metastatic nodules. Numerous lymphatic channels were seen leading to the tumor masses and carrying large quantities of gold. Along the periphery of these lymph nodes, and in some areas deeply infiltrated into the masses, were found accumulations of gold particles with definite tumor destruction. In these cases, however, the greatest concentration of radioactivity was found, not in the tumor masses and lymph nodes, but in the surrounding fatty tissues which were in immediate proximity to the areas injected.

It is well to point out that the radiation emitted from radioactive gold consists almost entirely of a beta ray whose effect is confined to a very limited periphery. This fact, plus its multiple pin point source uniformity, allows it to be used safely concomitantly with deep roentgen and radium therapy. As an example of the value of radioactive gold in localized therapy, we would like to describe another case not listed above. This patient had been treated for squamous cell carcinoma of the cervix. She had developed vaginal metastasis which had been treated with roentgen and radium therapy. In spite of the treatment, the metastases recurred as submucosal masses. It was not feasible to give these areas any more radiation therapy because the overlying skin and mucosa had already received more than tolerance levels. It was decided to inject radioactive gold into the tumor masses. Ten millicuries of radioactive gold were injected directly into one mass. Regression of the tumor mass occurred without a breakdown in the overlying tissue. In this case, a cancerocidal dose was delivered deep in the mass itself and, because of the localized effect of gold, the normal tissues surrounding the tumor were not over-irradiated.

The potentialities of the complementary use of radium with radioactive gold can therefore be visualized. Keeping in mind that even in an apparently early case, cancer cells may already have been carried to the outer parametrium, successful therapy will have to devitalize or remove these inaccessible cells. Surgery may in some cases reach the extended periphery of invasion but in most cases the tumor probably would be missed by the operation. Radium used in the present day manner, although quite effective in the treatment of the local lesion, fails to deliver an adequate dose to the lymph nodes and the cervical drainage regions. However, the cells in this zone would receive some influencing effect from the penetrative gamma rays. Roentgen therapy, as presently used, does not usually deliver a cancerocidal dose to the lymph nodes or the parametrial areas, but again adds more influencing effects. This leaves an area or rather a volume of tissue which is not effectively treated. Radioactive gold used in the manner described can effectively and safely treat this region by bolstering the total effect in the regional

lymph nodes as well as sterilizing the lymphatic drainage channels from the cervix.

This entire problem is vividly illustrated by 2 of the cases in this series. Cases v and vii, both considered as League of Nations Stage i, were found to have cancer cells far out in the parametrial tissues. The cells in these particular cases were well under control, however, by the presence of overwhelming encirclement by radioactive gold and showed the usual disintegrating changes associated with irradiation.

The value of the interstitial injection of gold was again illustrated at operation. It was found that some of these outlying irremovable tissues, far laterally on the pelvic wall and in intimate proximity to vital organs, showed definite evidence of the infiltration of gold.

These observations give some encouragement to the idea that radioactive gold may be used to irradiate the parametrium and thereby enhance the probability of cure whether the primary lesion is treated by radical surgical removal, by radium or roentgen therapy.

SUMMARY

Radioactive gold suspended in pectin solution was used interstitially alone and in conjunction with radium preoperatively in the treatment of carcinoma of the cervix uteri. It was also injected into the inguinal region previous to resection of these lymph nodes in carcinoma of the vulva.

The radioactive gold was found to enter the lymphatic system and reach the regional lymph nodes. There were definite irradiation effects noted both in the parametrium and in the corresponding lymph nodes.

Careful observation indicates that doses of radioactive gold, at the levels used here, were entirely within tolerance levels.

The results of these experiments qualify the use of radioactive colloidal gold as a supplementary treatment for carcinoma of the cervix and vulva and suggest the use of this material as an adjunct to present methods of radiation therapy in these diseases.

The authors wish to express their appreciation to Dr. Robert J. Crossen for permission to include his private patient in this paper.

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DISCUSSION

Dr. James F. Nolan, Los Angeles, California. It is very difficult to discuss this excellent presentation without using the trite phrase, "It represents very exciting potentialities." The triteness of that expression emphasizes one point which was brought out; namely, that this was a tracer experiment. The material was not used in these patients for the treatment of cancer—it was used, instead, to find out what happens to the radioactive gold. The results of this study are important. However, there are many other aspects that have yet to be explored. Tolerance levels are being studied in animals, but certainly adequate and safe dosage data have to be worked out much more thoroughly before this can be accepted as a therapeutic method in human subjects.

Beside that, there are other questions: Does the material go into lymph nodes that have cancer in them? If so, does it destroy the cancer that is in those lymph nodes? If so, does it do it completely? These questions, I feel sure, will be answered eventually by Drs. Sherman, Bonebrake and Allen.

The other point that I would emphasize is that it is obvious that the treatment means we have at hand today for the treatment of carcinoma of the cervix are not complete and adequate in all cases. We need whatever we can develop to help in the treatment of this disease.

The argument about surgery and irradiation goes on and on. The addition of radical surgery to radical irradiation has been a failure in most people's hands; but if we can develop irradiation means that may be fitted into a surgical regimen, or surgical measures that may be fitted into an irradiation regimen, we may get a higher total survival rate by the combination of these two rather than one against the other.

Dr. Hugh F. Hare, Boston, Massachusetts. In the animals studied was there an attempt to explain where the gold eventually traveled? Did you do any liver or spleen biopsies?

Dr. Sherman (closing). Yes. During the animal experimentations, liver and spleen were studied quite adequately. As you saw from the chart, the total blood circulating radioactivity was an index of how much was involved. Much less than one-quarter of 1 per cent of the entire amount injected did enter the entire circulating blood stream.

In the animal experiments there was some gold found in the liver and spleen, but not enough to cause any damage that we could notice by microscopic study. The animals survived and showed no reaction that we could see.

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DEPARTMENT OF TECHNIQUE

ROENTGENOLOGICAL STUDY OF THE FEMORAL NECK

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THE difficulty in obtaining a satisfactory roentgen examination of the hip in two projections in planes perpendicular to each other is evidenced by the several methods in common use today. Each of the routine techniques certainly has its definite useful place in the detailed study of the hip joint, femoral neck, and trochanteric region. We wish here to add a variation of the lateral projection of the hip commonly termed the "frog" position for study of the femoral neck in the lateral projection in those patients who can be placed readily in this position.

We chanced upon this procedure while

FIG. 1. Anteroposterior view of the left hip showing only a slight irregular increase in the density of the femur suggesting a slight impaction and a break in the cortex on the superior surface of the neck. Although these findings are indicative of a fracture the actual fracture line is not demonstrated.

FIG. 2. Routine lateral view of the fractured hip with the patient in supine position. The roentgen tube is placed under the opposite knee and the film is placed lateral to the ilium of the affected side for this projection. The fracture line is not demonstrated.

Fig. 3. Routine "frog" position using a perpendicular central ray. The femur is parallel to the table top with this projection. Note that the greater trochanter is superimposed on the lower half of the foreshortened femoral neck shadow.

examining a patient for question of a hip fracture. A very slight variation was noted in the cortex of the neck of the femur in the anteroposterior projection suggesting a fracture which, however, was not demonstrated on a Potter-Bucky film taken in the commonly used "frog" position. In this well known position the knee and the lower leg are supported in a comfortable position on sand bags with the lower leg in a horizontal position on the table and the central ray perpendicular to the table and centered over the femoral neck.

In an attempt to obtain a more satisfactory view of the femoral neck, a study of the skeleton was made which showed that a true projection of the femoral neck could be obtained if the knee of the affected leg was elevated so that an angle of 60° was subtended between the shaft of the femur and horizontal table top, and the lower leg was supported in the horizontal position on pillows or sandbags. In this position a roentgenogram of the femoral neck could be taken with the central ray directed through the mid femoral neck with a 15° cephalad tilt of the tube to separate the femoral neck from the overlying rim of the acetabulum in its upper portion and the greater trochanter at its base. The resulting roentgenogram of the hip is vastly superior in diagnostic value and fortunately can be used in the examination of those patients who have impacted fractures, incomplete fractures, or osteochondritis of the femoral neck, or slipped femoral epiphysis.

The lateral projection of the hip used in the examination of the stretcher and bed patient is usually of less diagnostic value than the view taken in the "frog" position. However, the radiologist is fortunately restricted to that procedure only when the derangement is obvious and the hip cannot be positioned for either the view described here, or the better known lateral

Fig. 4. The modified "frog" position described in this article. Note the well defined femoral neck shadow with relatively little superimposition of the acetabulum or greater trochanter.

Fig. 5. Photograph of a patient showing position during roentgenography of the hip in a modified frog position.

Fig. 6. Photograph of a skeleton during roentgenography of the hip in a modified frog position.

view without risking more damage. The stretcher technique should be used whenever there is a complete or non-impacted fracture of the hip.

To insure that no damage will be done to an obviously fractured hip when the weight of the pelvis is supported on the greater trochanter, we believe this modified technique should be used only after an anteroposterior film of the entire pelvis taken on 14 by 17 inch film has been examined. In deciding whether or not to use the procedure, the ability of the patient to assume the necessary position is a secondary criterion and should not be relied upon without first viewing a film of the pelvis.

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EDITORIALS

AGENESIS OF THE LUNG

AGENESIS of the lung is supposedly a rare condition, but with the increased number of reports that one finds in the literature it is probably of much more frequent occurrence than is believed; certainly with the widespread routine examinations of the chest, it is quite likely that this condition will be encountered more frequently. However, with the increase in the reports from various clinics and with the now well established methods of diagnosis of this particular condition it should be recognized more often than apparently it is. Numerous reports have occurred in the literature over the last several years.

In the article by Van Loon and Diamond[1] from the Chevalier Jackson Bronchoscopic Clinic in 1941 was reported apparently the third case of agenesis of the lung diagnosed before death. In a survey of the literature which they made at this time there were on record only forty genuine cases of this congenital anomaly. In June, 1942, Castellanos and Pereiras[2] of Cuba reported three additional cases, with a review of the literature, and in 1944 Ferguson and Neuhauser,[3] in an article on congenital absence of the lung (agenesis), reported five cases which had been diagnosed during life. Of these five cases, four were at the time of their report still living and well.

All authors reporting this relatively rare condition agree that the anomaly occurs more frequently in the male than in the female and it is noted more often on the left side than on the right. In the cases reported by Ferguson and Neuhauser three of their patients were females, and absence of the lung was found on the left side in three cases.

Various theories have been postulated as to the probable etiologic factor in the lack of development of a lung. Most observers agree that there must be an inherent defect in the germ plasm as there are so often associated other congenital anomalies; indeed, Ferguson and Neuhauser's five cases showed additional abnormalities of development.

The symptoms which these patients exhibit are so inconstant that careful roentgen studies plus bronchoscopy with lipiodol injection of the tracheobronchial tree and other methods of study are needed to bring about a correct diagnosis.

Schneider[4] has divided pulmonary agenesis into three types, depending on the age at which the developmental defect occurred. His classification, which is probably among the simplest, calls attention to three types: first, complete aplasia of the bronchus; second, small bronchus with no pulmonary tissue; and third, small bronchus and a small amount of pulmonary tissue. All observers agree that the third type is the least common and that the second type is the one most commonly seen.

Quite recently (1950) Ingram, Hudson and Davis,[5] in reporting two cases of aplasia of the lung diagnosed during life, called attention to a method of study which

[1] Van Loon, Emily L., and Diamond, S. Congenital absence of the right lung; its occurrence in a healthy child. *Am. J. Dis. Child.*, 1941, *62*, 584–589.

[2] Castellanos, A., and Pereiras, R. Pulmonary agenesia; report of 3 cases, and general review. *Bol. Soc. cubana de pediatria*, 1942, *14*, 268–330.

[3] Ferguson, C. F., and Neuhauser, E. B. D. Congenital absence of the lung (agenesis) and other anomalies of the tracheobronchial tree. Am. J. Roentgenol. & Rad. Therapy, 1944, *52*, 459–471.

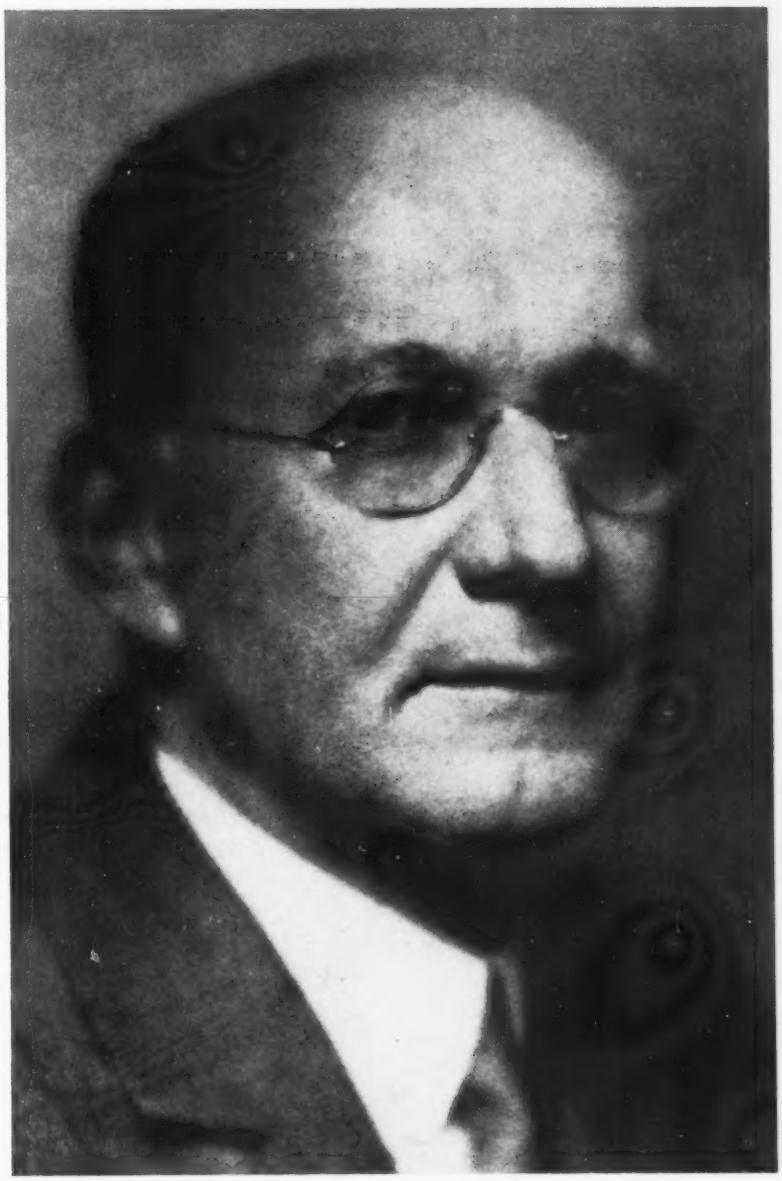
[4] Schneider, P. Quoted by Ingram, Hudson and Davis.[5]

[5] Ingram, M. D., Jr., Hudson, G. W., and Davis, T. J. Aplasia of the lung; with angiocardiographic demonstration of anomalous pulmonary circulation. Am. J. Roentgenol. & Rad. Therapy, Sept., 1950, *64*, 409–413.

they thought to be the first angiocardiographic demonstration of a single pulmonary artery. This belief that their demonstration by angiocardiographic methods was the first used in agenesis of the lung is in error as Castellanos and Pereiras (1942) in reporting three additional cases of agenesis of the lung, together with a review of the literature, called detailed attention to the various methods of exploration in the arrival at a positive diagnosis of agenesis of the lung, and pointed to the angiocardiographic method which they devised as a routine procedure in a study of the suspected cases. They point out that angiocardiography "insures visualization of the great vessels, leading to the heart, and springing from its cavities, and the large vessels originating in these cavities." In applying the angiocardiographic method in suspected cases of broncho-alveolar dysgenesia they have been able to demonstrate that there exists an angiocardiographic image which may be considered to be pathognomonic of pulmonary agenesia and severe broncho-alveolar hypoplasia. Up to the time of the report of Castellanos and Pereiras there were no data regarding the topography of the heart in these deformities, or the size of the heart or the relation between the heart volume and the other thoracic structures, or the arrangement of the afferent or efferent vessels in the living patient. In their report they pointed out that angiocardiography reveals in the living the same details which are found at operation or autopsy. Since angiocardiography is capable of demonstrating the presence of a single branch of the pulmonary artery, in every case of pulmonary agenesis, Castellanos and Pereiras consider it to be a very valuable method for establishing an exact diagnosis. They demonstrated that a great many of the cases presenting broncho-alveolar deformities also have some additional congenital cardiopathy and that angiocardiography furnishes the greatest number of details for the diagnosis of cardiovascular deformities, revealing as well the presence of pulmonary agenesis. This method of examination, Castellanos and Pereiras postulate, is of the utmost importance in the prognosis of the case.

It is interesting to note that Van Loon and Diamond, in the report of their case in 1941, state that "The roentgenographic observations strongly suggest that no pulmonary vessels are present on the right side but definite proof of the existence of such a vascular defect must await demonstration at autopsy," but within the span of a few years angiocardiography has reached such a point of appliçability in the hands of those trained in the technique that it may be employed as a special measure to supplement the other diagnostic procedures.

Thus Castellanos and Pereiras and, apparently independently, Ingram, Hudson and Davis have given us an additional and very valuable and extremely accurate means of arriving at a correct diagnosis in these supposedly relatively rare conditions. All authors agree that a guarded prognosis should be given but that the condition is compatible with longevity.



HARRY MILES IMBODEN

1878-1951

HARRY MILES IMBODEN, physician, roentgenologist, widely known in lay and professional circles, internationally acclaimed by his fellows, held in high and affectionate regard by all who knew him, died in New Rochelle Hospital, June 13, 1951.

He was born at Lebanon, Pennsylvania, August 23, 1878, the son of George W. and Amanda Killian Imboden. He received his Bachelor of Arts degree from Lebanon Valley College in 1899; the same college honored him with the Doctor of Science degree in 1935, at which time he was a mem-

ber of its governing body. He obtained the degree of Doctor of Medicine at Jefferson Medical College in 1903 and the following year served his internship at Methodist Hospital, Philadelphia, Pennsylvania.

Following this preliminary training, a period of several years was spent at Clifton Springs Sanitarium, Clifton Springs, New York, where he was resident physician from 1905 to 1911. It was there that Dr. Imboden became interested in diagnostic and therapeutic roentgenology. He practiced for a short period in Rochester, New York, before going to New York City to be associated in practice with Eugene Wilson Caldwell until Caldwell's death. The recognition of his skill as a roentgenologist and teacher resulted in his appointment as Visiting Physician, Presbyterian Hospital, X-ray Department, New York, New York, from 1918 to 1922. In 1923 he was made Professor of Roentgenology, Cornell University Medical College, retaining that post until his resignation in 1937. During all his years in New York City and until his death, Dr. Imboden was engaged in the private practice of roentgenology. For many years he was consulting Roentgenologist at Knickerbocker Hospital, New York Hospital, Hospital for Special Surgery and Beekman Street Hospital, as well as Flushing Hospital, Flushing, and Mount Vernon Hospital, Mount Vernon, New York.

He was a member of the Executive Council of the American Roentgen Ray Society for four years, serving as Chairman of the Council for one year, and in 1929 he was honored by being made President of the American Roentgen Ray Society.

Harry Imboden was a fellow of the New York Academy of Medicine, taking an active interest in the committee work of that organization; diplomate of the American Board of Radiology; councilor for the State of New York of the American College of Radiology; member of the New York Roentgen Society in which society he served two terms as President and one as Secretary; and fellow of the British Institute of Radiology.

During the years 1918 to 1922 he served with distinction as Editor of the American Journal of Roentgenology, and in 1923 as Editor of the American Journal of Roentgenology and Radium Therapy.

Though not a prolific writer, Dr. Imboden did publish important papers on the roentgen diagnosis of lesions of the vermiform appendix; spondylolisthesis; and progress in the development of roentgen-ray apparatus. Collaboration with Leopold Jaches and William H. Stewart resulted in the production of the *American Atlas of Stereoroentgenology*. Again, in collaboration with Howard F. Shattuck he wrote concerning chronic intermittent duodenal obstruction. He divulged the compass of his knowledge—anatomical, physiological, medical and roentgenological—when discussing cases with referring physicians. It was that capacity that brought his colleagues to his office for personal consultation and it was at those consultations that he demonstrated the influence which Eugene Wilson Caldwell had on his career.

Those who had the privilege of working with Dr. Imboden were impressed by his zeal for work. There seemed to be a driving force, urging him through each day as though he were attempting to repay in part a debt owed for his knowledge and understanding—surely he ended each day of work with the feeling that he had brought forth his best effort in attempting to solve the problems of that day.

He was always ready and willing to do anything he could to help solve the problem of a confrère, co-worker, or friend; never looking for recompense, in fact discouraging any effort to repay—he was actually a great physician, a noble soul. All who knew him, knew too of the admiration and esteem in which he was held by the leaders of the medical profession in which he attained the highest ranking.

Harry Imboden was first to recognize and praise ability—yet praise for himself and his countless efforts to help in solution of any problem was the last thing he wanted.

Always a hard worker, he was persuaded to take up golf when he approached the age of fifty—only those with whom he played know how much these hours of relaxation meant to him during the years he was physically able to play. Not a performer, he enjoyed to the utmost good music and good theater and spent many evenings of relaxation in attendance at concert, opera or play.

He lived without ostentation and wanted no recognition for his many philanthropies.

In April, 1906, he married Edith Grabill who died in 1915. In 1916 he married Florence Briggs, who survives him. He is survived also by a son, Henry M. Imboden, and by an elder sister, Mary E. Saylor of Annville, Pennsylvania.

In remembering him, a friend who sat with Harry on the Diaconate Board of his church, quoted, in recognition of his many benefits to mankind the following lines:

> And when he fell
> He went down as when a lordly
> cedar green with boughs,
> Goes down with a shout
> upon the hills,
> And leaves a lonesome place
> against the sky.

E. Forrest Merrill, M.D.

PEDRO ALBERTO BARCIA

1888-1951

PEDRO ALBERTO BARCIA, a gentleman, a teacher, a cosmopolitan, died on March 30, 1951, in Montevideo, Uruguay, of coronary thrombosis.

All radiologists in South America mourn his death because Barcia represented the outstanding radiologist, as founder and teacher of clinical radiology in the University of Montevideo.

Every year many young, as well as the trained radiologists from Brasil, Argentina, Chile, Paraguay and Bolivia, attended his lectures. This year, when he was about to start his courses, death crossed his path.

Pedro A. Barcia began his studies in radiology in 1911, gaining from the beginning much prestige with his work on roentgenographic anatomy in the Institute of Anatomy of Montevideo. He took his M.D. degree in 1914, starting immediately to work as radiologist in the University Hospital as an assistant of Professor Ricaldoni. In 1916 he presented an exhibit, complete with gross pathology and surgical results, that made him famous. In this same year he made his first trip to Europe, as a reward for his work. On the Continent he worked with Bensaude, Vasquez, Béclère and Solomon. By this time, the first units of the American Expeditionary Force arrived in Europe. He then had the good chance of meeting Professor James T. Case and remained with his group as an interpreter. When the First World War came to an end he visited the United States, obtaining from Graham, in St. Louis, the first shipment of tetraiodine for South America.

Back in Montevideo he began his career as a professor starting with a motto to which he remained faithful till his death: "A good radiologist has to be a good clinician."

In 1927 he returned to Europe but this time as an authority in his field, giving lectures in France, Sweden and England. In 1934 he published the book "Affections of the Lung" with the collaboration of Julio Garcia Otero and Nicolas Caubarrere. All his books have the collaboration of a clinician or a surgeon, and are well known among the Latin American doctors. These works include "Radiology of the Heart," "Carcinoma of the Lung," "Radiologic Study of the Gallbladder."

In recognition in North America of his outstanding work, Professor Barcia was made a Corresponding Member of the American Roentgen Ray Society in 1927, and at the 1950 meeting he was elected an Honorary Member of that organization.

In paying this final tribute to Professor Pedro Alberto Barcia, I wish to make known to all our American colleagues how great a man he was and what he represented for medicine, especially for radiology, in South America.

Mário Alves Filho

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Shoreham Hotel, Washington, D.C., Sept. 25–28, 1951.

American Radium Society
Secretary, Dr. J. E. Wirth, 635 Herkimer St., Pasadena 1, Calif. Annual meeting: Stevens Hotel, Chicago, Ill., June 8, 9 and 10, 1952.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y., Annual meeting: Palmer House, Chicago, Ill., Dec. 2–7, 1951.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6.

Section on Radiology, American Medical Association
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich.

Alabama Radiological Society
Secretary, Dr. W. W. Anderson, Tuscaloosa, Ala. Meets time and place Alabama State Medical Association.

Arizona Radiological Society
Secretary, Dr. R. Lee Foster, 507 Professional Building, Phoenix, Ariz. Two regular meetings a year. The annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Atlanta Radiological Society
Secretary, Dr. J. D. King, 35 Linden Ave., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

Brooklyn Roentgen Ray Society
Secretary, Dr. J. J. Daversa, 345 75th St., Brooklyn, N. Y. Meets monthly fourth Tuesday, Oct. through April.

Buffalo Radiological Society
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. F. A. Riebel, 15 West Goodale St., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, December, February, April, and June at Columbus Athletic Club, Columbus, Ohio.

Chicago Roentgen Society
Secretary, Dr. B. D. Braun, 6 N. Michigan Ave., Chicago 2, Ill. Meets second Thursday of each month, October to April inclusive at the University Club.

Cleveland Radiological Society
Secretary, Dr. Mortimer Lubert, 10515 Carnegie Ave., Cleveland 6, Ohio. Meetings at 6:45 P.M. on fourth Monday of each month from October to April.

Colorado Radiological Society
Secretary, Dr. Paul E. RePass, 306 Republic Bldg., Denver 2, Colo. Meets third Friday of each month at University of Colorado Medical Center or at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. E. W. Godfrey, 1676 Boulevard, West Hartford, Conn. Meets second Friday Oct. and April.

Dallas-Fort Worth Roentgen Study Club
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. J. C. Cook, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434-30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. Nelson T. Pearson, 1109 Huntington Bldg., Miami, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. R. C. Pendergrass, Americus, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

Greater Miami Radiological Society
Secretary, Dr. T. M. Berman, 350 Lincoln Rd., Miami Beach, Florida. Meets last Wednesday of each month at 8:00 P.M. at Veterans Administration Regional Office.

Houston Radiological Society
Secretary, Dr. F. M. Windrow, 1205 Hermann Professional Bldg., Houston, Texas. Meets fourth Monday each month.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. William M. Loehr, 712 Hume-Mansur Bldg., Indianapolis 4. Meets second Sunday in May.

Iowa X-Ray Club
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society.

Kansas Radiological Society
Secretary, Dr. Anthony F. Rossitto, Wichita Hospital, Wichita, Kan. Meets annually with State Medical Society.

Kentucky Radiological Society
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Wybren Hiemstra, 1414 S. Hope St., Los Angeles 15, Calif. Meets second Wednesday each month at Los Angeles County Medical Assn. Building.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

Maine Radiological Society
Secretary, Dr. C. F. Miller, Central Maine General Hospital, Lewiston, Maine.

Miami Valley Radiological Society
Secretary, Dr. G. A. Nicoll, 134 Apple St., Dayton, Ohio. Meets second Friday of fall and winter months.

* Secretaries of societies are requested to send timely information promptly to the Editor.

Michigan Association of Roentgenologists
Secretary, Dr. R. D. McDuff, 220 Genesee Bank Bldg., Flint 3, Mich.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, Sept. to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. T. J. Pfeffer, 839 N. Marshall St., Milwaukee 2, Wis. Meets monthly on second Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. L. A. Nash, 572 Lowry Medical Arts Bldg., St. Paul 2, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. John W. Evans, 621 High Street, Jackson 2, Miss. Meets third Thursday of each month at the Rotisserie Restaurant at 6:30 P.M.

Nebraska Radiological Society
Secretary, Dr. R. W. Blanchard, 1216 Medical Arts Bldg., Omaha, Nebr. Meets fourth Thursday of each month at 6 P.M. at Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. L. L. Robbins, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Harvard Club.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Irving Schwartz, 45E. 66th St., New York 21, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. J. E. Hemphill, 1420 E. Fifth St., Charlotte 4, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings by announcement.

Northeastern New York Radiological Society
Secretary, Dr. John F. Roach, Albany Hospital, Albany, N. Y. Meets four times a year, the times being announced by the Secretary.

Northern California Radiological Club
Secretary, Dr. G. A. Fricker, Sacramento County Hospital, Sacramento, Calif. Meets at dinner last Monday, every second month, except June, July and August.

Ohio State Radiological Society
Secretary, Dr. E. C. Elsey, 927 Carew Tower, Cincinnati 2, Ohio. Meets Ft. Hayes Hotel, Columbus, Ohio, May 25–27, 1951.

Oklahoma State Radiological Society
Secretary, Dr. W. E. Brown, 21st & Xanthus, Tulsa 4, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. J. Richard Raines, 214 Medical-Dental Bldg., Portland 5, Oregon. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport. Annual meeting: Bedford Springs Hotel, Bedford, Pa., May 16 and 17, 1952.

Philadelphia Roentgen Ray Society
Secretary, Dr. G. P. Keefer, American Oncologic Hospital, Philadelphia 4, Pa. Meets first Thursday each month October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary Dr. E. J. Euphrat, 3500 Fifth Ave., Pittsburgh 13, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Richard B. Hanchett, 705–6 Medical Arts Bldg., Baltimore, Md. Meets third Tuesday each month, Sept. to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Fred. Zaff, 135 Whitney Ave., New Haven, Conn. Meets bimonthly on second Wednesday.

Radiological Section, District of Columbia Medical Society
Secretary, Dr. W. M. Clopton, 3929 Oliver St. N.W., Washington 15, D. C. Meets Medical Society Auditorium, third Thursday, Jan., March, May, Oct. at 8:00 P.M.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of Greater Cincinnati
Secretary, Dr. L. J. Gibboney, 831 Carew Tower, Cincinnati 2, Ohio. Meets first Monday each month, at 7:30 P.M., September to May, inclusive.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of New Jersey
Secretary, Dr. Nicholas G. Demy, 912 Prospect Avenue, Plainfield, N. J. Meets annually at Atlantic City at time of State Medical Society and mid-winter at Elizabeth, N. J.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. George Gamsu, 191 S. Goodman St., Rochester, N. Y. Meets monthly on last Monday from September through May, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr. Meets August 9, 10, 11, 1951, Shirley-Savoy Hotel, Denver, Colorado.

St. Louis Society of Radiologists
Secretary, Dr. D. S. Bottom, 510 S. Kingshighway, St. Louis, Mo. Meets fourth Wednesday each month, except June, July, August, and September.

San Diego Roentgen Society
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Tuesday at dinner.

San Francisco Radiological Society
Secretary, Dr. I. J. Miller, 2680 Ocean Avenue, San Francisco 27, Calif. Meets quarterly.

Section on Radiology, California Medical Association
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. Harold L. Shinall, St. Joseph's Hospital, Bloomington, Ill.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Bay Radiological Society
Secretary, Dr. Charles E. Duisenberg, 300 Homer Avenue, Palo Alto, Calif. Meets second Tuesday each month.

South Carolina X-Ray Society
Secretary, Dr. Henry E. Plenge, Spartanburg General Hospital, Spartanburg, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, Newell Hospital, Chattanooga,

Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas. Meets Houston, Texas, Jan. 18 and 19, 1952.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. R. C. Kiltz, 705 Medical-Dental Bldg., Everett, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

Wisconsin Radiological Society
Secretary, Dr. Irving I. Cowan, 425 E. Wisconsin Ave., Milwaukee 2, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. M. A. Sisson, 450 Sutter St., San Francisco, 8, Calif. Meets Jan. to July, Lane Hall, Stanford Univ. Hospital; July to Dec. San Francisco Hospital.

Cuba, Mexico and Central America

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86 Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1.

Faculty of Radiologists
Honorary Secretary, Dr. J. F. Bromley, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Jean Bouchard, Suite 305, 1555 Summerhill Avenue, Montreal 26, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electrologie et de Radiologie Médicales
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

Australian and New Zealand Association of Radiologists
Honorary Secretary, Dr. Alan R. Colwell, 135 Macquarie St., Sydney, N.S.W.
Honorary Secretaries, State Branches:
New South Wales, Dr. E. W. Frecker, 135 Macquarie St., Sydney.
Victoria, Dr. T. L. Tyrer, 3 Lockerbie Court, East St. Kilda.
Queensland, Dr. J. Adam, 131 Wickham Terrace, Brisbane.
South Australia, Dr. R. de G. Burnard, 170 North Terrace, Adelaide.
Western Australia, Dr. A. M. Nelson, 179-B St. Georges Terrace, Perth.
New Zealand, Dr. E. G. Lynch, 12 Bolton St., Wellington.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mocsa, Avda. Gral Paz 151, Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central Buenos Aires
Secretary, Dr. Oscar F. Noguera, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro, Sede, Cordoba
President, Prof. Dr. David L. Caro, Corro 86, Cordoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte, Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza.
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Colombiana de Radiologia
Secretary, Dr. Alberto Torres Focke, Av. 34, No. 17–34, Bogota, Colombia. Meets last Wednesday of each month.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Sociedad de Radiologica, Cancerologia y Fisica Medica del Uruguay
Secretary, Dr. Arias Bellini, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Allies, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord

Secretary-General, Dr. A. Dariaux, 9 bis, Boulevard Rochechouart, Paris IX^e^, France.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10:30, X-Ray Dept., Akademia Gdansk.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad. USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Societa Italiana di Radiologia Medica
Secretary Prof. Mario Ponzio, Ospedale Mauriziano. Torino, Italy. Meets biannually.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India

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AMERICAN COLLEGE OF RADIOLOGY

At the Twenty-seventh Annual Meeting of the American College of Radiology held at the President Hotel, Atlantic City, New Jersey, on June 10, 1951, Dr. Robert R. Newell of San Francisco, California, was elected President of the College for 1951–1952 and Dr. Douglas Quick of New York, New York, was elected Vice-President.

Dr. Ira H. Lockwood, Kansas City, Missouri, and Dr. Warren W. Furey, Chicago, Illinois, were elected to four year terms on the Board of Chancellors. To represent the scientific societies on the Board of Chancellors, Dr. John D. Camp, Rochester, Minnesota, was re-elected to a two year term on the nomination of the Radiological Society of North America; Dr. George W. Grier, Pittsburgh, Pennsylvania, was re-elected to a one year term on the nomination of the American Roentgen Ray Society; and Dr. Hugh F. Hare, Boston, Massachusetts, was re-elected to a two year term on the nomination of the American Radium Society.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

The 118th Annual Meeting of the American Association for the Advancement of Science, which will be held in Philadelphia, Pennsylvania, December 26–31, 1951, will include programs of all eighteen of the Association's sections and about forty-five participating societies. Focus of the approximately 225 sessions will be Convention Hall, adjacent to the School of Medicine of the University of Pennsylvania and its associated hospitals. The headquarters hotel will be the Bellevue-Stratford.

The Subsection Nm-Medicine will have a four-session symposium on Abnormalities of Lipid Metabolism, with special reference to arteriosclerosis, on December 29 and 30, with a medical scientists' dinner on December 29. The Oak Ridge Institute of Nuclear Studies will have a two-session symposium on Radioisotopes in Medicine.

Detailed information in regard to the meeting can be secured by writing the American Association for the Advancement of Science, 1515 Massachusetts Avenue, N.W., Washington 5, D. C.

CONTINUATION COURSE IN ROENTGENOLOGY OF CHEST DISEASES

The University of Minnesota announces a Continuation Course in Roentgenology of Chest Diseases from October 29 to November 3, 1951. The course, which will be presented at the Center for Continuation

Study, is intended for radiologists. The material will include detailed anatomical and pathological studies of the chest presented by means of lectures and demonstrations. Correlation of this material with clinical and roentgenologic findings will be emphasized. Visiting faculty members of the course include Dr. W. Edward Chamberlain, Temple University, Philadelphia, Pa.; Dr. Chamberlain will also give the annual Leo G. Rigler Lecture in Radiology on the evening of Thursday, November 1; Dr. Benjamin Felson, University of Cincinnati, Cincinnati, Ohio; Dr. L. Henry Garland, Stanford University, San Francisco, Calif.; Dr. George R. Krause, Mount Sinai Hospital, Cleveland, Ohio; and Dr. Averill A. Liebow, Yale University, New Haven, Conn.

Chairman of the continuation course will be Dr. Leo G. Rigler, Professor and Head of the Department of Radiology, University of Minnesota Medical School. He will be joined by the members of the faculty of the University of Minnesota Medical School and the Mayo Foundation.

The enrollment for this course is limited. Those interested should write immediately to the Director, Center for Continuation Study, University of Minnesota, Minneapolis 14, Minnesota.

POSTGRADUATE TRAINING IN ORTHOPEDIC SURGERY

Physicians seeking postgraduate training in orthopedic surgery will have an opportunity to study at the Hospital for Joint Diseases, 1919 Madison Avenue, New York, New York. The course being offered in affiliation with Columbia University, College of Physicians and Surgeons, will consist of eleven morning and eleven afternoon sessions held on consecutive Thursdays, beginning September 27, 1951, and ending December 13, 1951. The curricula will include a series of lectures, case demonstrations and conferences on the clinical, diagnostic, therapeutic, pathologic, bacteriologic, chemical and radiologic aspects of skeletal disease, so integrated as to present a general review of the modern concept of the more important orthopedic diseases. There will be opportunity for clinical examination of patients.

ROENTGEN INTERPRETATION OF DISEASES OF BONES AND JOINTS

A postgraduate course in roentgenographic interpretation of the diseases of bones and joints will be held at the Hospital for Joint Diseases, 1919 Madison Avenue, New York, New York, in affiliation with Columbia University, College of Physicians and Surgeons from October 3 through December 19, 1951.

There will be a series of lectures covering the roentgenographic analysis of acute and chronic diseases of bones and joints including granulomas, neurotrophic lesions, neoplasms and the manifestations of nutritional and metabolic bone changes in children and adults.

The course will consist of a didactic lecture lasting about one hour and followed by a lantern slide demonstration illustrating the disease or diseases under discussion. An average of approximately thirty-five to fifty lantern slides will be shown at each session, all representing material selected from cases seen at the Hospital for Joint Diseases during the past twenty-five years.

OREGON RADIOLOGICAL SOCIETY

At a recent meeting of the Oregon Radiological Society the following officers were elected: *President*, Dr. Arthur F. Hunter, Portland; *Vice-President*, Dr. John R. Seeley, Eugene; *Secretary-Treasurer*, Dr. J. Richard Raines, Portland. The Society meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

PITTSBURGH ROENTGEN SOCIETY

At the meeting of the Pittsburgh Roentgen Society held June 13, 1951, the following officers were elected for 1951–1952: *President*, Dr. Lester M. J. Freedman; *Vice-President*, Dr. Joseph E. Malia; *Secretary*, Dr. Edwin J. Euphrat; *Treasurer*, Dr. Newton Hornick.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Diagnostic Roentgenology. Volume I. By Ross Golden, M.D., Editor, Professor of Radiology, the College of Physicians and Surgeons, Columbia University; Director of the Department of Radiologic Service, The Presbyterian Hospital, New York. Fourth issue of renewal pages. Thomas Nelson & Sons, 385 Madison Avenue, New York 17, New York, 1950.

The fourth issue of renewal pages for Diagnostic Roentgenology, edited by Ross Golden, consists of two sections. The first is entitled the "Roentgen-Ray Diagnosis of Diseases of the Skull and Intracranial Contents: Additional Considerations" by Arthur E. Childe; the second is a complete new section on the "Roentgenologic Diagnosis of Diseases of the Bones" by David G. Pugh. The first supplements the original section written by Cornelius G. Dyke. It contains descriptions of the author's technique for encephalography and ventriculography which differs from that originally described by Dyke in that all exposures are made with the patient in a horizontal position. The descriptions are given in greater detail than in the original contribution. Some of the subjects considered are supplements to those in the first edition such as the one on arteriography which is brought up to date. Others are descriptions of conditions not included in the original chapter. Line drawings are used to illustrate anatomical structures and special mention should be made of the pneumographic analysis charts of roentgenograms of several of the cases. The reproductions of the roentgenograms are excellent. All of them are negatives and almost all are of larger size than in the original edition. Several illustrations of pathological material are included.

Dyke's contribution was comprehensive and these additional considerations enhance its value. The bibliography is ample and consists of publications of the last decade, bringing this aspect of the work up to date. The chapter is now an excellent presentation of the roentgen aspects of the skull, and is more valuable because of Childe's supplement.

Pugh's contribution is a complete chapter on Diseases of the Bones and is to be substituted for the previous chapter which was written by Hodges, Phemister and Brunschwig. In the introduction, Pugh states that he has endeavored to emphasize the pathologic changes which occur in diseases of the bones and also the physiological alterations which take place. To this he has adhered. The descriptions of the various diseases are in some instances necessarily brief, but taken as a whole they are ample and furnish stimulation to seek further information in the literature if desired. The bibliography is sufficiently comprehensive and references to investigators and authors in various fields are listed under specific headings for the various diseases. This atones for the purposely omitted references to writers and investigators in the text.

The opening section is a description of the histopathology and physiology of bone and is followed by one on skeletal maturation. The list of bone diseases discussed is ample and consists of those which are of greatest importance and which are encountered most frequently. In fact, very few are omitted. Many new conditions are described such as infantile cortical hyperostosis, progressive diaphyseal dysplasia, and others.

If, at the time Diagnostic Roentgenology was published in 1936, it may have seemed too big for a textbook and too condensed for a reference book, such criticism is no longer justified. The renewals published since the first edition, together with the retained portions of the original text, constitute an accurate, well written and extremely useful book for the radiologist as well as for the student of radiology.

R. S. Bromer, M.D.

Arteriosclerosis and Arterial Thrombosis in the Lower Limb. A Roentgenological Study. Acta radiologica, Supplementum LXXX. By Åke Lindbom. Paper. Pp. 80, with 42 illustrations. Esselte Aktiebolag, Stockholm, Sweden, 1950.

This comprehensive monograph is the result of extensive roentgenologic studies of the arteries in the lower limbs of living patients and cadavers. The clinical subjects were examined

both by plain films of the thigh and leg and percutaneous femoral artery injection of 35 per cent diodrast followed by multiple exposures of the entire lower extremity. The postmortem specimens were injected with a special barium sulfate mixture and then careful dissection of the arterial branches thus filled carried out. Roentgenograms and microscopic sections of interesting areas of arterial disease aided in correlation of the roentgen appearance and pathologic features of diseased arteries as seen in living patients.

The investigation was mainly focused on advanced arterial lesions: (1) occlusion, (2) thickening of the wall, and (3) calcification in the wall.

Occlusion of an artery can be judged only on serial films during arteriography where there is seen slowing of the contrast stream through the involved segment. An indirect sign of arterial occlusion is the presence of contrast medium in vessels at the level of or below the area where there is non-filling of an arterial segment, indicating the presence of collateral circulation.

Intimal thickening is seen in arteriograms as a defect in the contrast column, and an intimal plaque of only 0.5 mm. height can be detected.

There are several types of calcification in peripheral arteries, the intimal calcium deposits being the clinically important ones as they are a sign of arteriosclerosis with considerable encroachment on the vessel lumen. This type of calcification is most common and most easily recognized in the femoral artery in the region of Hunter's canal on a plain soft tissue film made with the limb rotated outwards. Medial calcification is regular, diffuse and fine grained, generally affecting the whole circumference of the artery at an area of mechanical stress (*e.g.*, popliteal artery). The intima is rarely thickened in a part of an arterial wall in which there is medial calcification. Calcification of the internal elastic membrane is granulated with isolated grains limited to small sections of the vessels (usually found in the anterior tibial artery just above the ankle joint).

The earliest arterial lesion, the intimal hemorrhage, can be detected on arteriograms as an intimal cushion and serves probably as the source of an arterial thrombus which the author believes is the precursor of arterial occlusion.

The author's careful investigation has resulted in many interesting and important conceptions of arterial disease. This monograph, replete with excellent illustrations, should be read with interest by all clinicians and radiologists concerned with the ever-increasing opportunities for diagnosis and treatment of peripheral vascular disease.

Harold Fulton, M.D.

Bibliotheca Tuberculosea. Supplementa ad Schweizerische Zeitschrift für Tuberkulose. Revue Suisse de la Tuberculose. Volume IV. Bronchus et Pulmo in ihren klinischen Beziehungen. By Dr. med. A. Wernli-Hässig, Präsident der Zürcher Kantonalen Liga gegen die Tuberkulose. Pp. 176, with 131 illustrations. Price, bound sFr. 19.-; unbound sFr. 15.-. S. Karger, Holbeinstrasse 22, Basel, Switzerland, 1950.

This volume is a supplement of the *Schweizerische Zeitschrift für Tuberkulose* and *Revue Suisse de la Tuberculose*. It covers a symposium or a short course given to physicians on the subject by the Swiss Society to Combat Tuberculosis (Zürcher Kantonalen Liga gegen die Tuberkulose).

There are very complete and instructive discussions dealing with the diagnosis and treatment of disease of the lung and bronchi. In the introduction, Dr. A. Wernli-Hässig, President of the organization, emphasizes the importance of collaboration of the chest physician, radiologist, and surgeon in the management of lung and bronchial disease. He stresses particularly the importance of the general practitioner on the team, for he actually examines the patients first and must see that they get in the proper hands for the more complicated methods of diagnosis and therapy. He states that the purpose of this postgraduate course was in a sense to get the general practitioner interested in being a part of this team.

The first chapter concerns respiratory insufficiency. It is written by Klaus Wiesinger and stresses the importance of respiratory physiology.

A second chapter by W. Löffler discusses atelectasis. It is a very complete and illuminating chapter on this particular subject. Obstructive atelectasis in bronchial occlusion is discussed particularly well.

The third chapter has to do with the pathologic anatomy of the bronchi in tuberculosis. It is by E. Uehlinger. Bronchial tuberculosis is discussed in its various forms and with the roentgenologic and clinical manifestations.

The fourth chapter, by J. Steiger, discusses the differential diagnosis of various hilar

masses. Apparently this is not always easy or even possible from the roentgen-ray standpoint alone.

In the fifth chapter, E. Tanner has something further to say about bronchial tuberculosis. Both this chapter and the third emphasize the important place that bronchostenosis and atelectasis play in tuberculosis.

H. R. Schinz, in chapter six, discusses bronchography using ioduron B, a new water-soluble opaque material of high viscosity. There is a very rapid uptake of this new opaque substance. There is also less irritation from this material in the lung. The indications for bronchoscopy are discussed and a classification of the bronchial tree with a nomenclature is given.

There is also a chapter on cavity healing by L. Rüedi. He states that occlusion of the draining bronchus is essential to obtain a permanent result in the healing of a cavity.

Chapters are also included on bronchoscopy and the diagnosis of bronchiectasis.

Karl Mülly discusses intubation anesthesia in lung surgery. This chapter emphasizes that the dangers which were formerly attendant on lung surgery have, for the most part, been overcome, due to the better anesthesia management and preoperative and postoperative care; also treatment to forestall surgical shock during the operation.

The final chapter is by A. Brunner, who discusses the indications for lobectomy and pneumonectomy.

Altogether this supplement is a very interesting and valuable review of the subject.

Paul Swenson, M.D.

Photons and Electrons. By K. H. Spring, M.Sc. Cloth, $1.75. Pp. 108, with 38 diagrams. John Wiley & Sons, Inc., 440 Fourth Avenue, New York 16, New York, 1950.

This is one of the delightful little booklets of the Methuen's Monograph Series in Physical Subjects. This series intends to "supply readers of average scientific attainment with a compact statement of the modern position" in physics. The author of *Photons and Electrons* seems to have been rather successful in attaining this ambitious goal. In about one hundred pages of small format he discusses adequately the various ways in which electrons interact with radiation, without delving too deeply into the theoretical aspects of these phenomena. Fundamental considerations of the energies of electrons and photons, as well as theoretical ideas on waves and particles together with experimental measuring procedures, are presented in the opening chapter. These are followed by discussions of the photoelectric and Compton effects, electron-pair production and cosmic rays. Particular attention is paid to the interrelationship between theoretical and experimental aspects of the various phenomena. Thirty-eight excellent diagrams add considerably to the understanding of the lucid text and a comprehensive reference list helps the reader to pursue further any aspects he may be particularly interested in.

Otto Glasser, Ph.D.

Experimentelle Untersuchungen über Röntgeneffekte und chemische Effekte auf die pflanzliche Mitose. Von Dr. Med. Kurt Hohl. Paper. Pp. 87, with 30 illustrations and tables. George Thieme, Diemershaldenstrasse 47, Stuttgart, Germany, 1949.

The author undertook an experimental study dealing with the effect of roentgen rays (180 kv., 12 ma., 0.5 mm. Cu, 40 cm. focus-skin distance) and certain chemicals (as, for instance, urethane, higher alcohols, acetone and others) on mitoses in plants. Most of the observations were made on cells from the roots of a bean (*Vicia faba L.*) and in some instances an onion (*Allium cepa L.*). The method of fixation and preparation of the specimens for microscopic study are described in detail. The results obtained by the author are summarized as follows:

1. Roentgen irradiation of 25–600 r causes concentrations of thymonucleic acid in the chromosomal matrix (pyknosis of chromosomes); elimination of the centrosome's motility and fragmentation in the chromoneme. Three hundred to 600 r occasionally causes damage to the spindle as well; small doses (25–50 r) retard mitosis; larger doses (200–600 r) cause a temporary suspension of the mitotic process. All changes are dependent on dosage.

2. Chemical substances act through chemophysical or entirely through chemical processes. They act upon (1) the cytoplasm, (2) the "atractoplasm" (spindle apparatus), (3) the nuclear material. Again, all changes are dependent on dosage.

3. Effects having similar points of attack may be summated.

4. Chromosomal pyknosis is a nonspecific change inasmuch as it can be produced by irra-

diation and chemical substances as well as solely by processes resulting in dehydration.

5. Chromosomal fragmentation following changes in molecular structure could be accomplished only through roentgen irradiation.

6. The elimination of the centrosome is a "hit reaction," and is produced both by irradiation and by chemical substances.

7. The temporary suspension of mitosis is a nonspecific process, and can be produced by roentgen irradiation as well as by different substances.

8. The inhibition of early metaphase is a nonspecific process and is produced by a disturbance in the synthesis of the matrix which can be caused both by roentgen rays and by chemical substances.

9. Inhibition of late metaphase (injury to the spindle apparatus) can be caused either by a nonspecific chemophysical or by a specific chemical reaction.

10. A prolongation of the course of mitosis between prophase and anaphase—that is, in the duration of the metaphase—leads to a reversible chromosomal shortening (a nonspecific process).

The illustrations for the most part represent photomicrographs of pathologic mitosis; a bibliography is appended.

Ernst A. Pohle, M.D.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Abdomen

Carnahan, D. S., Jr. Primary hepatoma with metastasis to a long bone. *Radiology*, Dec., 1950, *55*, 844–847.

Primary carcinoma of the liver occurs either as a hepatoma or intrahepatic bile duct tumor, with hepatoma being by far the most common.

Bone metastases from a hepatoma are not common and occur in from 1 to 8 per cent of all cases. A case is reported in which the metastatic lesion was evident as a fracture of the right humerus with subsequent tumor formation. Later a mass appeared in the cervical area and a biopsy revealed thyroid tissue which the pathologist had difficulty differentiating from carcinoma. The liver became palpable and the enlargement was thought due to thyroid carcinoma metastases. Only at postmortem examination was the hepatoma discovered. Review of the pathologic material showed that the bone tumor and cervical tumor bore a striking resemblance to the hepatoma.—*C. A. Stevenson, M.D.*

Moser, Marvin, Sheehan, George, and Schwinger, Harold. Pheochromocytoma with calcification simulating cholelithiasis; report of a case. *Radiology*, Dec., 1950, *55*, 855–858.

A case is reported where an annular area of calcification about 2 cm. in diameter within a pheochromocytoma was thought to be a gallstone until ruled otherwise by studies using contrast medium. The clinical findings were consistent with pheochromocytoma but surgery was refused and the impression was verified after death due to the complications of hypertension. Reports of such cases in the literature are rare.—*M. B. Goodwin, M.D.*

Arrieta Sánchez, L. Dos casos de hepatoesplenografía con thorotrast, inyectados hace 16 y 14 años, respectivamente. (Two cases of hepatolienography with thorotrast injected sixteen and fourteen years ago respectively.) *Radiología*, Dec., 1950, *1*, 26–30.

In 1928 and 1929 Oka and Radt were the first to visualize the liver and spleen by means of intravenous injection of thorium dioxide. Since then thorotrast has been used as an opaque medium especially for cerebral arteriography and, less frequently, for the demonstration of selected lesions of the liver and spleen. In Panama thorotrast was used in 1930 in 50 patients.

In the present article, the author describes in detail 2 cases in which thorotrast was used for hepatolienography.

In the first case, the injection was made sixteen years ago, and the patient now has an atrophic cirrhosis of the liver. Roentgenograms still show good visualization of the liver and spleen. In addition, there are several supplementary shadows in the upper part of the abdomen, representing no doubt uptake of the thorotrast by the portocaval lymphoid system, as well as the regional lymph nodes.

In the second case the injection was made fourteen years ago, apparently with a smaller dose, the opacification of the liver and spleen is here less marked and there are only sparse shadows in the regional lymphoid tissues. This patient presented himself for examination because of intermittent pain in the right upper quadrant of fifteen years' duration, more pronounced when he would partake of excessive alcohol. A cholecystographic examination revealed non-visualization of the gallbladder.

The cases are described with the purpose of proving that the injection of thorotrast as an opaque medium may lead to marked late changes due to the fact that it is permanently retained by the cells of the reticulo-endothelial system.

The author uses this occasion to also call attention to a new method of "oral hepatography" described by Olson and Ekman at the University of Lund in 1949. This method is based on the fact that fatty acids absorbed from the intestine are partially resynthesized in the liver, hence the possibility of combining halogens with fatty acids which then produce opacification of the liver. Bromine appears to be the most suitable halogen. Olson and Ekman injected by means of a tube 1 to 4 ml. of emulsified bromide in sesame oil into the stomach of rats. Within twenty-four hours, marked accumulation of this substance was noted in the liver lasting for two to twelve hours, after which time the liver became less and less opaque on roentgen observation. The opaque substance was also seen in the capsule of the kidney, in the retroperitoneal fat, in the fat deposits of the pelvis, and to a lesser extent in the spleen. It is hoped that this method will permit roentgenologic study of the mode of digestion of the fats in the alimentary canal and of the fat metabolism in general. So far, all the investigations have been made in animals but it is anticipated that the method will also prove successful in man, thus permitting hepatography to be performed without the dangers inherent in thorotrast.—*T. Leucutia, M.D.*

Gottlieb, Charles, and Beranbaum, Samuel L. Gastric residue in cholecystography. *Am. J. Digest. Dis.*, Dec., 1950, *17*, 389–394.

The authors have observed 7 cases showing retention of priodax in the stomach at the time of cholecystography. Priodax is absorbed in the small bowel in an alkaline medium and not from the stomach. Its retention in the stomach would indicate a delay in emptying of the stomach.

Five of the 7 cases had organic pathology in the stomach or duodenum. The authors stress the importance of observing the stomach for priodax in cases of non-visualization of the gallbladder since its presence may be secondary to delayed emptying of the stomach.—*V. L. Peterson, M.D.*

Crenshaw, James F. Dysfunctioning, noncalculous gallbladder. *Am. J. Digest. Dis.*, Dec., 1950, *17*, 387–389.

The cholecystographic finding of a gallbladder with normal dye concentration but sluggish emptying with or without evidence of abnormality is a problem of great interest to the gastroenterologist and surgeon.

The author found 107 cases falling in this group in a routine study of 500 cases. An attempt was made to evaluate the finding of less than 50 per cent emptying in three hours after a fatty meal.

In this group all patients had some form of digestive disturbance although only 35 per cent showed typical gallbladder symptoms. Gastric analysis in 69 showed less than 15° free HCl in 36 per cent. Low basal metabolic rate was present in 50 per cent of 54 cases in which a metabolic test was performed.

Treatment in each case has been medical without surgical intervention. Surgery, it is believed, is indicated only after all conservative medical measures have failed.—*V. L. Peterson, M.D.*

Haden, W. Dan, Jr. Annular pancreas; a case report. *Radiology*, Dec., 1950, *55*, 859–860.

Annular pancreas is of rare occurrence and preoperative diagnosis is almost unheard of. Most cases are discovered on the operating table or at autopsy.

A case report of a $3\frac{1}{2}$ year old white male is presented with accompanying roentgenograms. The child had complained of intermittent epigastric pain for at least one year.

At the original examination, the only abnormality noted was a slight dilatation of the first portion and proximal part of the second portion of the duodenum. There was a smoothly margined defect about 1 cm. in length in the mid-part of the second portion of the duodenum. Passage of the barium through this segment was delayed. There was no abnormality noted below this level.

A repeat examination three weeks later showed no change.

Annular pancreas was strongly suspected and at operation a ring of pancreatic tissue, from the head of the pancreas, was found completely encircling the second portion of the duodenum. A section of the tissue was removed. Five months later only a slight residual deformity of the duodenum was found.—*E. M. Cooper, M.D.*

Ravitch, Mark M., and Woods, Alan C., Jr. Annular pancreas. *Ann. Surg.*, Dec., 1950, *132*, 1116–1127.

Annular pancreas is described as an uncommon anomaly consisting of a thin, flat band of apparently normal pancreatic tissue continuous with the head of the pancreas and encircling the second portion of the duodenum. Often the anterior portion of the band contains a duct which connects with the main pancreatic duct. In many instances, this band lies loosely upon the duodenum and may be lifted away from it, thus distinguishing it from the anomaly "aberrant pancreas" in which pancreatic tissue actually is imbedded within the walls of the stomach, jejunum or ileum.

The condition occurs, in most instances, without producing symptoms and is discovered only at necropsy. When symptoms are produced, they usually occur late in life, a fact which is certainly unusual with anomalies of the gastrointestinal tract. Of 17 cases requiring surgical intervention and including the 3 reported in this paper, only 4 were in the neonatal period. These manifest themselves with the signs of high gastrointestinal tract obstruction. In adults, the frank obstruction may be preceded by the appearance of indigestion, eructation and vague epigastric pain, perhaps of some duration. The diagnosis can be made by barium studies in which characteristically there is an almost complete, smooth and sharp obstruction of the duodenum in its second portion. In view of the rarity of the condition, apparently the correct diagnosis is often missed. Erroneous diagnoses made in the past include arteriomesenteric ileus, cholecystitis, primary carcinoma of the duodenum, cicatrizing peptic ulcer, malrotation of the bowel and duodenal atresia.

Surgery is the only treatment to correct the high obstruction and has consisted in the past of division of the annulus or short circuiting anastomoses or combinations of the two procedures. Direct attack upon the anomalous pancreas introduces the hazards of pancreatic fistulae or of pancreatitis and apparently does not assure that the obstruction will be relieved.

The authors report 3 cases of annular pancreas, 2 in the neonatal period, and all successfully treated by short circuiting procedures. They feel that duodenojejunostomy is probably the method of choice.—*J. A. Martin, M.D.*

Pygott, F. Radiological appearances in pancreatic cancer. *Brit. J. Radiol.*, Nov., 1950, *23*, 656–666.

Of a series of 42 patients with carcinoma of the pancreas seen in four years, and proved with either operation or autopsy, 25 were examined with a barium meal. Of these 25, 9 showed no evident ab-

normality and 16 showed deformity which was due to the presence of the tumor. Among the 9 patients without roentgen changes, there were 5 who had large masses within the pancreas.

In patients where the head of the pancreas alone was involved, the barium study showed enlargement of the duodenal loop, pyloric obstruction, or deformity of the descending duodenum, but the degree of deformity was no indication of the size of the tumor. When the head and body were involved, enlargement of the duodenal loop or infiltration of the gastric wall associated with ulceration was seen. When the body alone was involved, a mass displacing the stomach upward, displacement of the stomach to the right with involvement of the greater curvature, or obstruction of the inferior horizontal duodenal segment was seen. When the entire gland was involved the mass deformed the medial portion of the lesser curvature, widened the duodenal loop, or compressed the inferior transverse duodenum.

From his data the author concludes that a negative examination does not exclude the possibility of even a large tumor. Also, a slight deformity may be very important when correlated with the clinical findings. He notes that enlargement of the duodenal loop may be due to lesions other than tumors of the pancreas.—*E. F. Lang, M.D.*

Eagle, J. Frederick, Jr., and Barrett, George S. Congenital deficiency of abdominal musculature with associated genitourinary abnormalities: a syndrome. *Pediatrics*, Nov., 1950, *6*, 721–736.

Forty-three cases of a syndrome of congenital deficiency of the abdominal musculature with associated genitourinary abnormalities have been reported. The authors add an additional 6 cases seen by them. The syndrome consists of partial or complete deficiency of the abdominal musculature and obstructive phenomena of the genitourinary tract limited only to enlargement of the urinary bladder or with hydroureter and hydronephrosis. Only 1 reported case was in a female, and the testes were undescended in all but 2 of the male cases. Frequently associated conditions are persistent urachus, pigeon breast chest deformity, and some form of talipes.

Most cases died at an early age of urinary tract infections. The authors report their 6 cases in detail and review the literature and pathogenesis. The authors favor the theory of Stumme in regard to pathogenesis. He postulated that the bladder became obstructed in utero, at or distal to the vesical neck. Accumulation of urine in the bladder caused distention with secondary hydroureter and hydronephrosis. Pressure of the dilated urinary bladder caused atrophy of the abdominal muscles by direct pressure or interference with blood supply. This also prevents descent of the testicles. The arguments for and against this theory are discussed.

With the advent of modern chemotherapy the infection which previously led to early deaths in these cases can be controlled. The problems to be dealt with now are the genitourinary anomalies and the weakened abdominal wall. Relief of genitourinary tract obstruction is an immediate problem. Primary recognition of the abdominal wall defects demands immediate investigation of the genitourinary tract for anomalies.—*R. M. Harvey, M.D.*

Littner, Michael. Aberrant pancreatic tissue in the first portion of the duodenum. *Radiology*, Nov., 1950, *55*, 716–719.

Aberrant pancreatic tissue is being reported with increasing frequency and is often responsible for symptoms which are sometimes severe. It is regarded as being due to a developmental error and is usually found in the first portion of the duodenum.

The aberrant tissue is characteristically found in the form of a single firm, sessile, intramural nodule, most commonly confused with a duodenal ulcer roentgenologically. The defect usually shows no mobility.

The author presents a case report of a twenty-four year old white male with a "heterotopic pancreas (accessory pancreas)" in the first portion of the duodenum.—*E. M. Cooper, M.D.*

Bertram, Harold F. Nonoperative treatment of perforated duodenal ulcer; preliminary report of 16 consecutive cases with no mortality. *Ann. Surg.*, Dec., 1950, *132*, 1075–1085.

The author instituted non-operative treatment of perforated duodenal ulcer because of (1) the undesirably high mortality rate of the operative treatment, (2) the incidence of complications and the prolonged morbidity attending the surgical procedure and (3) the availability of antibiotic and chemotherapeutic drugs to combat peritoneal infection.

Non-operative treatment of perforated duodenal ulcer is not a simple method of treatment and should not be handled casually. The cases must be supervised by a surgeon who is experienced in the care of patients with peritonitis in order that complications may be detected early and treated promptly. The most important single element in the non-operative treatment is the maintenance of constant gastric suction by means of the Levin tube. The gastric aspiration apparatus must function properly and must be checked by an experienced nurse at least every half hour. Continuous gastric aspiration is started as soon as the diagnosis is established. The importance of a correct diagnosis is obvious and unless the diagnosis is definite and unquestionable, surgical exploration should be performed.

Determination of the blood chloride level, carbon dioxide combining power, plasma protein and he-

matocrit, serum amylase and complete blood counts are essential laboratory procedures. An accurate recording of the fluid intake and output is also necessary. These procedures provide information which is helpful in determining the type and amount of intravenous fluids to be given.

Nothing is given by mouth and if there are no contraindications such as cardiac or renal disease, the patient receives 3,000 cc. of fluid intravenously during the first twenty-four hours. This consists of 1,000 cc. of 5 per cent glucose in distilled water; 1,000 cc. of one-sixth molar sodium lactate solution and 1,000 cc. of casein hydrolysate. Physiologic saline (1,000 cc.) is substituted for one of the above, depending on the blood chloride level. On succeeding days protein in the form of casein hydrolysate, whole blood or serum albumin is given to spare the body proteins, depending upon the blood chemistry findings and the intake and output record.

The medications administered consist of sodium sulfadiazine, 2 gm. intravenously, immediately and 1 gm. every four hours thereafter. Penicillin, in doses of 50,000 to 100,000 units, is given intramuscularly every three hours. In addition, intravenous injections of 100 mg. of thiamin chloride, 100 mg. of nicotinamide and 300 mg. of ascorbic acid are given daily.

One ounce of milk and cream mixture is given orally every hour beginning on the fourth to the sixth day with the Levin tube in place but clamped off. If this is tolerated and no signs of peritoneal irritation result the tube is withdrawn and the patient is gradually placed on an ulcer regimen.

Twenty-two patients were treated by this method. Six patients who recovered without complications were not reported because neither free intraperitoneal air nor evidence of a duodenal ulcer was demonstrated. The remaining 16 consecutive cases all showed duodenal ulceration on roentgenologic examination and 13 of the 16 had evidence of free intraperitoneal air on the roentgenogram. All of these patients recovered and the sole complication was a subphrenic abscess which was treated surgically.

Non-operative treatment of perforated duodenal ulcer is indeed revolutionary. The author believes that conclusions based on this small series are unjustified but that the excellent results warrant the continuance of this method of treatment until the series is large enough to allow definite conclusions.—*Gerald Lavner, M.D.*

Rosenburg, Gustave. Diverticula of the stomach. *Am. J. Digest. Dis.*, Nov., 1950, *17*, 373–377.

Rosenburg reports a case of diverticulum of the stomach and reviews the incidence, symptoms, differential diagnosis, anatomy and pathology, development, and therapy of the condition.

The case reported was a forty year old woman with numerous and varied gastrointestinal complaints. During the prior ten years several gastrointestinal studies failed to reveal abnormalities and she had been classified as a psychosomatic problem. However, another roentgenological examination revealed a large diverticulum arising from the lesser curvature, just below the cardia, retentive at twenty-four hours.

Since medical treatment did not bring relief, the patient was operated upon, at which time a paper-thin diverticulum was exposed and treated by inversion. At latest report, fifteen months after surgery symptoms have disappeared and she is considered to be cured.—*A. A. Brewer, M.D.*

Lampert, Elmer Graham, Waugh, John M., and Dockerty, Malcolm B. The incidence of malignancy in gastric ulcers believed preoperatively to be benign. *Surg., Gynec. & Obst.*, Dec., 1950, *91*, 673–679.

The study of this series of 73 cases of malignant disease of the stomach illustrates a well defined type of case for which there is no method of diagnosis short of the pathologic examination of the tissues removed. Symptoms, symptom-complexes, signs, laboratory examinations and tests all failed to indicate definitely the malignant or benign nature of these lesions. Even cancers of the stomach behaved in a manner not to be distinguished from benign ulcers when observed and treated medically. The results obtained indicated that the duration of symptoms was usually long; that many of the gastric lesions were associated with duodenal ulcer; and that a high percentage had one or more gastric hemorrhages. Acute perforation of a gastric cancer occurred in the group. Though all lesions were considered operable the resectability rate was 82.2 per cent. Slightly less than half of the patients lived five or more years. Of patients operated on for gastric ulcer at the Mayo Clinic from 1938 through 1942, 13 per cent actually had cancer. Temporizing with an ulcerating lesion of the stomach, therefore, introduces a serious risk.—*Mary Frances Vastine, M.D.*

France, Charles J., and Brines, Osborne A. Mesenchymal tumors of the stomach. *Arch. Surg.*, Dec., 1950, *61*, 1019–1035.

The authors have made a study of the tumors of the stomach encountered at the Detroit Receiving Hospital in the years 1922 to 1948. Mesenchymal tumors are those which originate from structures other than the surface lining mucosa and glands. Such tumors arise from muscle, connective tissue, fat, nerve, blood vessels and lymphoid tissue. They may be benign or malignant. The authors include lymphoblastomas in their classification, but not in

their series analyzed. There were 35 cases of mesenchymal gastric tumors, constituting an incidence of 9.8 per cent of all gastric neoplasms during this period. Of the 35 mesenchymal tumors, 57 per cent were benign and 43 per cent were malignant. The five year survival rate following resection of malignant mesenchymal tumor of the stomach is about 25 to 35 per cent, which is considerably better than that for cancer of the stomach.

The authors point out that there is little in the clinical picture or roentgen appearance to differentiate these tumors from one another, and that it is extremely difficult even for the pathologist to distinguish accurately between the benign and malignant forms.—*C. L. Hinkel, M.D.*

Weeder, S. Dana, and Stayman, Joseph W., Jr. Neurogenic tumor of the stomach; case report. *Ann. Surg.*, Dec., 1950, *132*, 1154–1157.

A case of an unusually large, benign neurogenic tumor of the gastric fundus in a forty-five year old white male is reported, with a brief review of the available literature on the subject. Clinically, such lesions behave much as any benign stomach tumor and are characterized by frequent episodes of hemorrhage without associated cachexia. The roentgenographic appearance may be characteristic but the final diagnosis depends upon histopathological examination. The authors emphasize four points: (1) growth is usually slow; (2) malignant change is not common; (3) metastasis is rare; but (4) local recurrence following excision is frequent. The case reported by the authors was classified histopathologically as a neurilemmoma. Following resection, the patient obtained complete symptomatic relief and was reported well approximately three years after the operation.—*J. A. Martin, M.D.*

Lee, C. Marshall, Jr., and MacMillan, Bruce G. The fallacy in the diagnosis of microcolon in the newborn. *Radiology*, Dec., 1950, *55*, 807–813.

The authors decry the use of the term "microcolon" because of the fact that the physician assumes that this is a hopeless congenital anomaly and that death will ensue shortly after the diagnosis is made.

The article emphasizes that microcolon does not imply a disease of the existing small colon but indicates a proximal obstruction either from congenital atresia or meconium ileus. Surgical correction of the atresia will relieve the obstruction and in time the small colon will enlarge and function normally.

The roentgen finding of a small colon with a lumen the caliber of a lead pencil means that during intrauterine life meconium did not get into the colon and hence the colon never "had a chance" to distend. When such a condition exists prompt search should be made for the obstruction and surgical correction done as soon as possible. A case bearing out this precept is reported. There was a "microcolon" up to the splenic flexure. At this site the surgeon relieved a congenital atresia and in the following months the "microcolon" enlarged to a normal size and functioned normally.

The term "microcolon" should be abandoned or reserved for descriptive term only.—*C. A. Stevenson, M.D.*

Berridge, F. R. The radiological examination of the small intestine. *Med. Illustrated*, Sept., 1950, *4*, 445–452.

The author finds the oral administration of barium satisfactory in most cases, although the Miller-Abbott tube may be used to advantage when there is intestinal obstruction and the terminal ileum can be examined by the barium enema. Normally the valvulae conniventes are highest in the upper jejunum and from there onwards they gradually diminish in height and become more widely separated. Distention cannot completely flatten these folds in the jejunum but it can in the ileum.

The so-called "deficiency pattern," for which Golden later substituted the phrase "disordered motor function," is seen in the small bowel of undernourished persons whether the undernutrition is due to incomplete intestinal absorption such as occurs in sprue, idiopathic steatorrhoea, celiac disease, cystic fibrosis of the pancreas and kwashiorkor, or to a diet deficient in calories. It has also been observed in hookworm disease, nephrosis and in a few other conditions which are usually not considered to be a cause or result of undernutrition. Both these terms are objectionable, the latter because no definite disorder of motor function has ever been proved to occur in the diseases concerned.

The abnormalities are listed under eight headings.

1. The transit time from the stomach to the cecum is usually prolonged.

2. The caliber of the bowel is usually wider than normal, especially in the upper jejunum.

3. The valvulae conniventes are more widely spaced than in normal persons, probably due to atony. In advanced cases of chronic idiopathic steatorrhea the outlines of the duodenal and upper jejunal loops may be smooth due to mucosal atrophy and some elongation of the gut.

4. The barium may appear to be mottled and less opaque than normal probably due to mixing with abnormal intestinal contents.

5. Gas and fluid levels may be present in the upper jejunum, probably due to ileus.

6. Segmentation may be present most commonly in the middle third of the small bowel. The author considers this to be due to clumping or flocculation of the barium by intestinal mucin. Sometimes all the barium is flocculated in the stomach.

7. Irregular scattered flecks of barium may remain

in the jejunum after the main meal has passed on. This is probably due to small fragments of flocculated barium and to clogging of the spaces between the mucosal folds by secretion.

8. Barium may move in a jerky manner through the jejunum, probably resulting from altered consistency due to flocculation by mucin.

In the acute stage of regional enteritis the only abnormality seen is slight irregularity of the mucosal folds. In the chronic stage the affected part of the bowel is narrow and rigid and the mucosal folds are irregular. Terminal ileitis usually stops short at the ileocecal valve in distinction to tuberculous disease which usually involves the cecum.

Adenocarcinoma is by far the commonest type of tumor of the small intestine.

Multiple diverticulosis of the small intestine may simulate the deficiency pattern and sometimes it is accompanied by steatorrhea, when there will be a typical deficiency pattern in addition to diverticulosis.—*A. E. Childe, M.D.*

Gynecology and Obstetrics

Moloy, Howard C., and Steer, Charles M. A new method of quantitative estimation of cephalopelvic disproportion. *Am. J. Obst. & Gynec.*, Nov., 1950, *60*, 1135–1146.

A method of using the precision stereoscope and circular disks with graduated diameters of 0.25 cm. to measure the dimensions of the pelvic inlet and fetal head is described. If the difference between the diameters of these two measurements is 1.0 cm. or less, the probability of cesarean section is 5:1. This probability decreases to zero when there is a difference of 1.8 cm. or more. It is interesting that in 58 cases of absolute disproportion (i.e., difference at the inlet of 1.0 cm. or less) only 5 normal children were delivered from below. Charts and discussion of the various degrees of disproportion are included.

In mid-pelvic disproportion, in addition to the above measurements (now at the level of the ischial spines), the characteristics of the sacrum and subpubic arch enter into the prognostication. The means of evaluating disproportion at this level is outlined.

At the Sloane Hospital for Women, only 11 per cent of cesarean sections were done for bony disproportion.

The quality of labor and the moldability of the fetal head are two factors which precludes absolute prognostication of the probability of cesarean section from the roentgenographic measurements alone. Both clinical and roentgenographic findings should be given proper, but not exclusive, consideration before the final course of delivery is chosen.—*J. D. Reeves, M.D.*

Flokstrumpf, Mieczyslaw. El embarazo y el cáncer de los organos genitales y mama. (Pregnancy and cancer of the genital organs and breast.) *Semana méd.*, Dec. 21, 1950, *57*, 1189–1195.

The author analyzes the relationship between pregnancy and cancer of the genital organs and of the breast based on a study of 809 women observed on the Radium Therapy Service at the Hospital Emilio Civit, Mendoza.

A statistical compilation of the age distribution revealed that cancer of the cervix and breast occurs in 6.2 and 4.6 per cent respectively between the ages of twenty-one and thirty years, in 20.2 and 22.8 per cent respectively between the ages of thirty-one and forty years, in 33 per cent of both between the ages of forty-one and fifty years, and in 25.9 and 20.9 per cent respectively between the ages of fifty-one and sixty years. Carcinoma of the body of the uterus makes its appearance somewhat later, the incidence between the ages of thirty-one and forty years being 8.7 per cent and from then on remaining about the same for the following three decades (a total of 78.2 per cent for the three decades).

The majority of the patients with cancer of the cervix and of the breast were multiparous (83.5 and 69.7 per cent respectively), whereas carcinoma of the body of the uterus occurred more frequently in the nulliparous (70.2 per cent).

The surprising fact is that a combination of pregnancy and carcinoma of the cervix occurred in 11.4 per cent and a combination of pregnancy and carcinoma of the breast in 9.7 per cent. There was not one single case of carcinoma of the body of the uterus complicated by pregnancy.

The author recommends the following procedure of treatment when cancer is complicated by pregnancy: (a) for carcinoma of the cervix, interruption of pregnancy followed by radium therapy; (b) for carcinoma of the breast, interruption of pregnancy, radical amputation of the breast, castration by means of roentgen therapy and hormonal therapy. Five year cures have been obtained in a certain number of both lesions.

Carcinoma of the vulva and vagina, malignant tumors of the ovary, and sarcoma of the uterus always led to fatal termination when complicated by pregnancy.—*T. Leucutia, M.D.*

Haines, Magnus, and Jackson, Ian. Granulosa-cell tumour of the ovary; an analysis of 40 cases. *J. Obst. & Gynaec. Brit. Emp.*, Oct., 1950, *57*, 737–746.

This group of 40 cases was collected in a survey of clinical and pathological material over a period of seventeen years. Sixty per cent of cases were in the 5th and 6th decades; 30 per cent were in women of child bearing age. Symptoms were chiefly uterine bleeding and pain. Swelling of the abdomen and

amenorrhea were found in several cases. Nearly all patients had a pelvic swelling. Ascites was not uncommon.

The tumors varied in size from 27 cm. in diameter to 2.5 cm. in diameter. There were bilateral tumors in 17.5 per cent. Malignancy as judged by cytology was difficult to assess. In 2 cases in which the tumor reappeared in the neck after seven years and in the groin after thirteen years, respectively, there were no features, in the sections of the primary ovarian tumors or in the metastasis which were suggestive of malignant disease.

The recurrence rate in the traced cases was 53 per cent and the mortality 45 per cent. The recurrences occurred in the reproductive, menopausal and post menopausal groups. Distant spread was rare and blood borne metastasis occurred in only 2 cases. Local spread appeared in the form of peritoneal nodules or retroperitoneal tumors.

One case of malignant granulosa cell tumor occurred in a girl fifteen years of age. Despite this the authors state that malignancy in these tumors is rare under the age of forty and that, provided there is no clinical spread, surgery should be conservative. If this is done, however, the case should be followed carefully for a long time. In women over forty years bilateral oophorectomy and a total hysterectomy is advised as recurrences are usually local.

The place of radiation therapy is discussed. The authors state that in view of the sensitivity of granulosa cells to radiation it might be thought that granulosa cell tumors would be very radiosensitive. Although it was felt that the physiologic function of the granulosa cells to produce estrin is easily depressed, it was difficult nevertheless to destroy the neoplastic tendency of these tumors. Eight cases in the series received deep roentgen therapy. Four of these, all with evidence of spread at operation, died. Of the 4 that were still living, the first was alive one year after operation at which time ascites and early local metastasis were found. In the second case, fifteen years after bilateral salpingo-oophorectomy, enlarged lymph nodes in the right groin and a soft mass in the left side of the pelvis quickly disappeared following deep roentgen therapy and one year later, no recurrence was found. The third case was treated by irradiation after salpingo-oophorectomy, at which time adherence to the omentum and small intestine, and ascites were found. The patient was free of recurrence for two years. The fourth case was treated by total hysterectomy with removal of both ovaries for an adherent left ovarian tumor. Seven years later, a granulosa cell tumor was removed from the left side of the neck. A swelling in the left hypochondrium was treated and made to disappear with deep roentgen therapy. One year later, there was no evidence of disease.

The authors feel that irradiation should be used following operation whenever there is local spread or metastasis.—*H. H. Galston, M.D.*

Merivale, W. H. H. A case of masculinovoblastoma. *Brit. M. J.*, March 17, 1951, *1*, 560–563.

The name "masculinovoblastoma" was suggested by Rottino and McGrath (1939) for a group of masculinizing ovarian tumors, consisting of large cells which often contain lipoid material and which resemble those of adrenal cortex or corpus luteum. Such tumors are histopathologically distinct from arrhenoblastomas.

The case of masculinovoblastoma described by the author demonstrated the syndrome of defeminization and masculinization in an advanced degree. On clinical grounds, a diagnosis of Cushing's syndrome was unlikely in view of the absence of striae, obesity, and hypertension, although the erythrocyanotic facies, hirsutism, and slight polycythemia were suggestive. Roentgenologically there was no osteoporosis. The pituitary fossa was of normal size, and no bony or intrathoracic abnormality was revealed. Hyperostosis of the skull which has previously been reported as a feature of masculinovoblastoma was absent in this case. The excretion of 11-oxycorticosteroids which is often increased in Cushing's syndrome and tumors of the suprarenal cortex was normal. The excretion of 17-ketosteroids was slightly increased. This militated against a diagnosis of suprarenal cortical tumor in which very high levels of excretion are usually encountered. The excretion of pregnanediol before operation was 2 mg. a day. Pregnanediol is excreted in measurable quantities in the urine during the luteal phase of the menstrual cycle and during pregnancy and is not excreted after the menopause, or only in very small amounts. This was significant since the patient's menses ceased at the age of thirty and she was sixty-two years of age at the time of this report. These findings led to a tentative diagnosis of adrenal type ovarian tumor.

Operation revealed an enlarged ovary in which normal ovarian tissue had been completely replaced by a tumor consisting of cells which resembled adrenal cortical tissue and therefore was designated a masculinovoblastoma.—*K. K. Latteier, M.D.*

Reagan, James W. The ovarian Brenner tumor; its gross and microscopic pathology. *Am. J. Obst. & Gynec.*, Dec., 1950, *60*, 1315–1323.

The purpose of this investigation was to study the pathology and histogenesis of the neoplasm utilizing 23 available specimens.

The Brenner tumor is an uncommon benign ovarian neoplasm which is usually unilateral in location. The solid or cystic tumors vary in size from microscopic to a reported specimen weighing 6.8 kilograms. They are composed of polyhedral cells arranged in masses and columns frequently surrounded by degenerated and hyalinized connective tissue. They

are to be differentiated from ovarian fibromas and thecomas.

There is suggestive evidence that this tumor may stem from so-called Walthard inclusion cells. The association of the Brenner tumor with other ovarian neoplasms is mentioned and was present in 3 of the cases of the series. A struma ovarii was present in 1 patient with bilateral Brenner tumor while in another case a serous cystadenoma was in proximity to a unilateral Brenner tumor. It is thought by some (Meyer, Novak, Jones) that the pseudomucinous cystadenoma may arise from this tumor.—*H. H. Calston, M.D.*

Douglas, Gordon Watkins, and Studdiford, William E. The diagnosis of early carcinoma of the cervix. *Surg., Gynec. & Obst.*, Dec., 1950, *91*, 728–741.

Since April, 1947, 16 cases of preclinical carcinoma of the cervix have been discovered at Bellevue Hospital; 13 were intraepithelial, 3 early invasive tumors. The pathology has been reviewed and certain features pointed out which are of value in their recognition.

The clinical details and the gross appearance of the cervix in these patients has been summarized in the article. The importance of metrorrhagia as a symptom is stressed.

The prime importance of random biopsy and of cell smears in arriving at a diagnosis has been brought out. These diagnostic aids reinforce each other and must be used together.

It is believed that knowledge of the lesion, the use of smears to detect its presence, and of biopsy and currettage to define the character and extent, should, when applied on a large scale, change greatly the present day end results of carcinoma of the cervix.—*Mary Frances Vastine, M.D.*

Asherman, Joseph G. Traumatic intra-uterine adhesions. *J. Obst. & Gynaec. Brit. Emp.*, Dec., 1950, *57*, 892–896.

A uterine cavity distorted by adhesions is a poor nest for the ovum and may cause spontaneous interruption of pregnancy.

Uterine curettage may be followed by conglutination of opposing uterine walls which produces no clinical symptoms. However, the diagnosis is readily made by hysterography. The treatment is surgical and consists in separating the adhesions.

The author describes his technique for preventing adhesions after curettage as well as the surgical treatment once such adhesions have formed. He points out that every case of habitual abortion, or sterility following abortion, must be examined roentgenologically.—*J. D. Reeves, M.D.*

Marshak, Richard H., Goldberger, Morris A., and Epstein, William A. Value of hysterography in the diagnosis of large submucous uterine fibroids. *Radiology*, Nov., 1950, *55*, 725–727.

Large submucous fibroids, when they occupy the entire uterine cavity, form a false smooth wall and are difficult to detect by curettage. Three case reports are presented in which curettage done because of abnormal bleeding showed no evidence of any tumor within the uterine cavity. Subsequent hysterograms, however, revealed filling defects typical of a submucous tumor.

Rayopaque and skiodan acacia were the contrast media employed. No ill effects were observed from the use of the drugs in this series.—*E. M. Cooper, M.D.*

Genitourinary System

Vesey, John, Dotter, Charles T., and Steinberg, Israel. Nephrography: simplified technic. *Radiology*, Dec., 1950, *55*, 827–833.

Nephrography is defined as the artificial method of increasing the density and contrast of the kidneys. This can be accomplished by: (1) abdominal aortography, (2) intravenous pyelography with ureteral obstruction, and (3) rapid intravenous injection of concentrated organic iodide solutions. This last method is explained in detail.

If the sensitivity test is negative, a special large-bore 50 cc. syringe is filled with the contrast substance (neo-iopax, 75 per cent, or diodrast, 70 per cent) and attached to the Robb-Steinberg No. 12 gauge needle inserted into an anticubital vein. The patient is instructed to breathe out and then inspire deeply. During the deep inspiration, the entire contents of the syringe are discharged in less than two seconds. Approximately sixteen to twenty-two seconds later a roentgenographic exposure of the abdomen is made followed by a second exposure of another film as soon as possible. The patient is then allowed to breathe normally. Delayed films may be made if desired for demonstration of the calyces and ureters.

There are three phases in nephrography: (1) The arterial phase, during which the contrast substance fills the renal arteries and their branches (between 10 to 14 seconds after the injection). (2) The capillary phase then follows and is the period of maximum opacification. This period lasts from four to six seconds. (3) The excretory phase begins during the preceding phase and lasts for several minutes.

This examination is of value in the differential diagnosis of renal cysts and malignant tumors. Renal cysts generally produce areas of radiolucency in the opaque renal shadow. The authors warn that apparent avascularity of a renal lesion might be considered indicative but not diagnostic of benign cyst.

Five illustrative cases with accompanying roentgenograms are presented.—*E. M. Cooper, M.D.*

Sabatini, S. A., and Wessler, Gerald. Retrocaval ureter; case report. *Urol. & Cutan. Rev.*, Dec., 1950, *54*, 720–721.

This is a rare anomaly, and the case herein described represents the forty-first instance of this condition reported in the literature up to the present time.

The patient, a male, aged sixty-three, complained of pain in the right lumbar region radiating into the right anterior abdomen. There was some tenderness on palpation of the right upper abdomen. On cystoscopic examination the bladder was normal, except for some prostatic encroachment. The ureters were catheterized and 10 cc. of 20 per cent skiodan injected in both sides. The pyelogram on the right side showed an "S" deformity of the upper third of the ureter; the middle third of the ureter was displaced toward the midline. There was rather marked hydronephrosis and hydroureter above the "S" shaped deformity. The clinical and roentgen findings were compatible with a retrocaval ureter.

At operation, a right nephrectomy and partial ureterectomy were done.—*G. W. Chamberlin, M.D.*

Weinberg, S. J., Goodman, J. R., and Bushard, M. C. Alterations in renal function, including hematuria, in man during intracranial air studies. *Arch. Int. Med.*, Dec., 1950, *86*, 857–871.

The question of the relationship between the central nervous system and the kidney is of great significance and involves not only somatic vasomotor and endocrine shifts in water balance but possibilities in nephritis as well.

Occurrence of oliguria following ventriculography and encephalography leads one to believe that a direct relationship may exist between central nervous stimulation and total suppression of renal output.

A series of studies was performed on patients routinely scheduled for ventriculograms and pneumoencephalograms. In 10 male patients undergoing controlled diuresis, the air studies were accompanied by antidiuresis, reduction in output of urinary chloride and nitrogen and, in several instances, electrocardiographic changes. In the majority of these patients red blood cells, white blood cells, round epithelial cells and, in 1 case, albumin, were seen in the urine during antidiuresis.

Evidence obtained supports the hypothesis that the urinary fluctuation in chloride, urea and volume are independent, each constituent having its own control mechanism.

The evidence favoring a central regulating mechanism responsible for anuria and nephritis is discussed.—*F. B. Markunas, M.D.*

Kretschmer, Herman L. Cancer of the kidney. *Urol. & Cutan. Rev.*, Nov., 1950, *54*, 641–644.

The author notes that, for practical considerations, all tumors of the kidney should be considered as malignant. Cancer of the kidney occurs in two age periods—namely, in infancy and childhood, and in the aging adult. Hematuria occurs in 40 per cent of the patients with renal carcinoma. The pain which is present usually consists of a dull ache in the flank. A tumor mass may be palpated but is usually a late sign. Other late signs are loss of weight and strength. Urinary symptoms related to the bladder may be due to infection or irritation by blood or pieces of tissue.

Intravenous urography is a routine procedure in all cases in which a tentative diagnosis of cancer has been made. However, all patients should have a cystoscopic examination and retrograde pyelograms. The Papanicolaou test may be of some value in the diagnosis of renal carcinoma. Bilateral renal carcinoma and renal carcinoma in association with calculus, tuberculosis, hydronephrosis, and polycystic disease may occur, but is uncommon.

The treatment of primary carcinoma of the kidney in patients with embryonal carcinoma is usually irradiation followed by nephrectomy. In those patients in the adult age group who have primary carcinoma of the kidney, the recommended treatment is nephrectomy. Roentgen therapy is noted to have very little value in the treatment of this type of carcinoma.—*G. W. Chamberlin, M.D.*

Swartz, David, and Taylor, J. Reid. Urinary calculi associated with recumbency. *Canad. M. A. J.*, Dec., 1950, *63*, 559–563.

The authors have reviewed the case histories of 1,500 patients immobilized for various periods of time in splints or plaster for spinal cord injury producing paralysis. Of these, 25 individuals developed urinary calculi.

The authors discuss the early mobilization of calcium salts from immobilized bone as well as the mechanism of calculus formation. The so-called "calcium sand" or "mud stones" are at first loosely packed and not attached to the renal pelvis or calyceal mucosa. There is almost complete absence of symptomatology when such calculi begin to form, and clinicians must be on the alert to recognize the early symptom of hematuria or the beginning calcium deposition which can be found on roentgenological study of the abdomen.

Treatment consists of the administration of adequate fluids, a diet rich in vitamins A and B, the maintenance of an acid urine, the control of infection, and frequent and regular changes in position which are intended to combat urinary stasis.

If a stone is recognized before consolidation has occurred, retrograde irrigation with G solution is often efficacious. If the "mud stone" cannot be dislodged or dissolved, it may be necessary to resort to surgical removal, irrigation through a nephrostomy tube or even nephrectomy in advanced cases.—*C. L. Hinkel, M.D.*

Winsbury-White, H. P., Henderson, D. St. C. L., and Wilkins, R. D. Simple papillomata of the bladder. *Lancet*, Dec. 16, 1950, *2*, 797–799.

In a series of 260 bladder tumors, 85 were obviously malignant and 31, though at first thought to be simple papillomas, proved to be malignant.

The papillomatous lesions occur more frequently as age progresses up the 6th and 7th decades of life and are approximately three times as frequent in the male as in the female.

The authors stress the importance of routine follow-up studies, first every four weeks, then every three months, and each year thereafter. Cystoscopic fulguration is recommended for all cases of papilloma of the bladder which appear to be simple, and at first, in all doubtful cases as a diagnostic measure. Implantation of radium or radon by the suprapubic route is successful in many malignant cases.—*V. L. Peterson, M.D.*

Skeletal System

Schmid-Schmidsfelden, O. Unsere Erfahrungen mit der "Knochenbank." (Our experiences with the "bone bank.") *Wien. klin. Wchnschr.*, Dec. 29, 1950, *62*, 977–979.

Homologous grafts were employed in 41 patients. Healing by primary intention occurred in 38 cases. There was 1 fistula, 1 case with prolonged secretion, and 1 infection presumably due to excess metallic fixation. The material obtained from amputations, osteotomies, and from fresh cadavers was dissected free from the soft tissue structures without disturbing the periosteum and was refrigerated at 2–4° C. for periods of one to twenty-eight days, four weeks being the absolute maximum. Strict asepsis was observed in obtaining and transplanting the graft material. The blood grouping was ascertained for both donor and recipient even though this precaution was probably unimportant. The Rh factor was determined, especially in premenopausal recipients. The age of the donors ranged from thirteen to forty-eight years. The operations included 20 arthrodeses, 12 grafts to bridge large bone defects, and 9 in which spongy bone (chips) was used.—*Joseph Zausner, M.D.*

Jackson, Harris. The diagnosis of minimal atlanto-axial subluxation. *Brit. J. Radiol.*, Nov., 1950, *23*, 672–674.

A series of 50 normal adult individuals was roentgenographed in lateral view with the neck in flexion and in extension to determine the distance between the posterior border of the arch of the atlas and the anterior border of the odontoid process of the axis. There was no change in the distance with change in the position of the head, and the distance did not exceed 2.5 mm. Twenty children were examined in the same way and in most the limits of normal appeared to be 2 to 2.5 mm. in extension and 2 to 3 mm. in flexion. One apparently normal child presented measurements of 2.5 and 4.5 mm.

Widening of the joint spacing may occur as a result of injury or on the basis of post-traumatic hyperemic softening of the transverse ligament of the atlas. The clinical picture of softening of the ligament can exist without manifest displacement.—*E. F. Lang, M.D.*

Cocchi, Umberto. Spondylosis deformans und Rheumatismus. (Spondylosis deformans and rheumatism.) *Radiol. clin.*, Nov., 1950, *19*, 351–364.

The question of relationship between spondylosis deformans and rheumatism is a problem which is not as yet fully elucidated. The pain and rigidity accompanying these conditions are usually attributed to morphologic alterations of the spinal column which are considered as static manifestations of wear and tear. There is no proof, however, that these morphologic alterations are exclusively the sequelae of inflammatory processes affecting the spinal column or that they are directly responsible for the clinical symptoms.

Stimulated by the large material available at the Central Roentgen Institute of the University of Zürich, the author examined the roentgenograms of the cervical spine in 1,017 unselected cases and has coordinated the roentgenolgoic findings with the clinical symptoms, incidence of age distribution, and occupation of the patients.

The results of this investigation are summarized as follows:

(1) The anatomo-roentgenologic demonstration of spondylosis deformans cervicalis may be associated with an entirely silent clinical course.

(2) There is a definite age proportionality in the incidence of the lesion, confirming the theory of wear and tear.

(3) The anatomo-roentgenologic changes of spondylosis deformans cervicalis may be accompanied by symptoms of chronic rheumatism.

(4) There is a definite age-proportionality also in the onset of the symptoms.

(5) Symptoms of chronic rheumatism may also be observed without the anatomo-roentgenologic alterations of the spondylosis deformans.

(6) In patients afflicted with chronic rheumatism the morphologic picture of spondylosis deformans cervicalis makes its appearance at an earlier age and more frequently than in non-rheumatic subjects.

(7) This is a confirmation of the fact that rheumatism hastens the wear and tear.

(8) Rheumatism exhibits climatic rather than occupational dependence.

(9) The anatomo-roentgenologic spondylosis deformans is not necessarily a sign of chronic rheuma-

tism; it can also develop without it.—*T. Leucutia, M.D.*

Bogdan, Andrew, and Clark, Justin. The manubrio-sternal joint in rheumatoid arthritis. *Brit. M. J.*, Dec. 16, 1950, *2*, 1361–1362.

Involvement of the manubriosternal joint by rheumatoid arthritis is not uncommon. The authors present 5 case reports emphasizing the clinical and roentgenological features.

The significant clinical findings were: pain, swelling, and tenderness of the joint region. Pain may be the first symptom and is aggravated by respiratory movement, coughing, sneezing, yawning and by exertion.

The significant roentgenological findings in advanced cases were: soft tissue swelling, irregularity and narrowing of the joint space, erosion of the articular surfaces, and irregular expansion of the articulating ends. Progression of the process to bony ankylosis was not observed in the authors' cases. Bony ankylosis may occur in normal persons but when it does the continuity of the bony surfaces is quite smooth.

The manubriosternal joint can best be demonstrated in the coned lateral views. Calcification of the costal cartilages and deformity of the sternum may prevent good visualization.—*C. W. Cooley, M.D.*

Riecker, Herman H., Neel, James V., and Test, Avery. The inheritance of spondylitis rhizomelique (ankylosing spondylitis) in the K. family. *Ann. Int. Med.*, Nov., 1950, *33*, 1254–1273.

The authors define the condition and give credit to the early men describing it. They point out that hereditary factors are of demonstrated importance in the etiology of hypertrophic arthritis, the arthritis of gout, rheumatic fever, and some of the mixed arthritides. Evidence for a hereditary factor in the etiology of rheumatoid arthritis has been scant. Spondylitis rhizomelique has resembled other types of rheumatoid arthritis in the poor definition of hereditary factors.

The criteria for diagnosis of spondylitis rhizomelique rest on the clinical history of low back pain, with onset usually in the twenties, the finding of a rigid "poker spine," an elevated erythrocyte sedimentation rate, and a characteristic roentgen picture of obliteration of the sacroiliac joints and calcification of the paravertebral ligaments.

The authors then discuss fully a pedigree in which a female who probably developed spondylitis rhizomelique in her late thirties, and whose mother and sister were probably likewise affected, gave birth to 13 children, 1 of which was dead. Three of the 12, ranging in age from thirty-six to fifty-nine have definite spondylitis rhizomelique. Of the remaining 9 children, 1 woman has the symptomatology and the Heberden's nodes characteristic of mild to moderate hypertrophic arthritis. One woman developed generalized arthralgia for six months, considered to be "menopausal arthralgia." Two persons have been subject to severe backaches.

From this survey the following deductions are made: That in two generations there occurred 5 proved cases of spondylitis rhizomelique, with a strong possibility that the trait extends back an additional two generations. This is a greater concentration in one kindred than can reasonably be attributed to chance.

A comparable situation has been reported for one other form of arthritis, Legg-Calvé-Perthes disease.

The etiological relationship of traumatic and tuberculous arthritis to ankylosing spondylitis is problematical, but the 4 other cases of "arthritis," all differing in important clinical respects from each other, raise the question of the possibility of an "arthritic diathesis," characterized by an unusual susceptibility of the articular surfaces to various influences in the external and internal environment, the exact nature of which is not yet clear.

The ratio of affected males to females is noteworthy. In standard works on arthritis the ratio of males to females in spondylitis is placed at about 9:1. The pedigree studied by the author shows 2 males to 3 females and becomes more unusual if the 3 possible affected females about whom less definite information was obtained are included.

The condition often goes unrecognized in its early stages, and this is unfortunate in view of the high degree of relief resulting from prompt roentgen therapy. When the diagnosis of ankylosing spondylitis has been reached in a patient, the clinician may view with appropriate suspicion any other members of the kindred, especially siblings and children of affected persons, presenting the symptom of backache. —*R. D. Moreton, M.D.*

Alexander, Gilbert H., and Mansuy, Matthew M. Disseminated bone tuberculosis (so-called multiple cystic tuberculosis.) *Radiology*, Dec., 1950, *55*, 839–843.

A case of disseminated bone tuberculosis is presented in an effort to clarify the problem of diagnosis in regard to the term osteitis tuberculosa multiplex cystoides originally reported by Jüngling, in 1920. This original description listed cyst-like areas, frequently found in the bones of the hands and feet, negative tuberculin test, absence of tubercle bacilli, absence of caseation and the frequent association of skin lesions.

Since this classic description, many cases have been reported which have all the criteria of disseminated bone tuberculosis or Boeck's sarcoid, but still grouped as osteitis tuberculosa multiplex

cystoides. Apparently Jüngling's disease should be considered osteal sarcoid and not bone tuberculosis. In Jüngling's disease the small bones of the hands and feet are affected while most proved cases of bone tuberculosis involve the long bones and occur in children. One or more bones may be involved but usually not the hands or feet.

A case of disseminated bone tuberculosis in an adult is reported. The skull and vertebral column were involved in contrast to the usual long bone localization in other reported cases. Biopsy of a diseased vertebra was necessary for diagnosis as the skull and vertebral findings suggested myeloma and eosinophilic granuloma in addition to the possibility of tuberculosis.—*C. A. Stevenson, M.D.*

Stewart, Marcus J., and Hamel, H. A. Solitary bone cyst. *South. M. J.*, Nov., 1950, *43*, 927–936.

The authors present 46 cases of solitary bone cysts with a discussion and evaluation of the various forms of treatment. The solitary bone cyst occurs, primarily in the metaphyseal region of the long bones and when it is adjacent to the epiphyseal plate, it is designated as being in the "active phase," whereas if it lies distant from the epiphysis it is assumed to be in the "latent phase." Most of the patients in this series had pain as the chief complaint and 50 per cent had pathological fractures.

The most common sites of involvement are the proximal portions, of the humerus, femur or tibia. The flat bones are seldom affected, although one patient in this series had a bone cyst in the wing of the ilium. Four of the cases had lesions in the os calcis.

The roentgen changes are an area of central bone destruction with expansile smooth walls and irregular lines of trabeculae across the cavity. The cortex is uninterrupted; periosteal new bone production occurs only at the site of a pathologic fracture. The intact cortex suggests the benignity of the lesion. Roughening of the cortex, periosteal proliferation with radiating spicules, or an osteolytic appearance of the cortex is more indicative of a malignancy.

One of the most important roentgenographic features of the cyst is its location on the metaphyseal side of the epiphyseal plate. In none of the cases presented was there any involvement of the epiphysis. A giant cell tumor invariably begins in the epiphysis and there is a great tendency for it to show asymmetrical enlargement, extensive involvement and perforation of the cortex. There is apparently less resistance to expansion and growth in the epiphysis.

The differential diagnosis is concerned primarily with giant cell tumor, malignancy, Brodie's abscess, gumma of bone and enchondroma.

The gross and microscopic appearance is briefly discussed. Histopathologically the cortex consists of loosely arranged osseous tissue permeated by dilated, thin walled vessels surrounded by giant cells.

The forms of treatment used were as follows: no treatment except for pathologic fracture when present, 14 cases; irradiation only, 3 cases; and surgery the initial procedure in the remaining cases. The various surgical procedures consisted of curettage only in 5 cases, curettage and chemical curettage in 2 cases, curettage with bone chips in 17 cases, curettage, cauterization and bone chips in 4 cases and resection in 1 case.

The authors feel that radiation therapy is not indicated in treatment of these lesions other than for adults with a cyst located in an inaccessible area, and they state that this form of treatment is contraindicated in children if the lesion is located near the epiphyseal line. In the 3 cases treated by roentgen therapy in this series, the results were graded as excellent with good anatomical and functional healing in 2 and only fair in the third. In this latter case there was a poor anatomical healing with shortening, limitation of motion, fibrosis and atrophy of muscles of the extremity. None of the cases showed better than fair filling in of the cyst cavity.

In general, it is concluded from this series that if resection is not practical, the most reliable treatment is thorough curettage of the cyst and its walls followed by cauterization with 95 per cent alcohol or phenol and alcohol, rinsing with saline and packing the cavity with autogenous or bone-bank bone.

There are numerous roentgenograms, tables and photomicrographs.—*J. G. Snead, M.D.*

Berardinelli, W. Two cases of Albright's syndrome observed in Brazil. *J. Clin. Endocrinol.*, Nov., 1950, *10*, 1499–1510.

The author reports 2 cases of Albright's syndrome observed in Brazil. Both were girls, one fifteen months, the other 5½ years old. Both showed very early precocious puberty—one menstruated at seven months, the other at fourteen months. Both presented extensive cutaneous pigmentations, blue sclerae and advanced bone age. In both girls there was a macrocytic anemia including lymphocytosis and eosinophilia. The mothers also presented cutaneous pigmentation and early menstruation (at the ages of ten and eleven years).—*C. P. Galanti, M.D.*

Phemister, Dallas B. Infarctus unique ou multiple des os chez l'adulte résultat d'une obstruction vasculaire aseptique. (Single or multiple infarcts of the bones in the adult, resulting from an aseptic vascular obstruction.) *Presse méd.*, Dec. 25, 1950, *58*, 1430–1433.

Discussing solitary and multiple bone infarcts due

to aseptic vascular obstruction, the author states that more than 200 cases have been reported and that this condition is recognized as a pathologic, roentgenologic, and clinical entity. The condition is more frequent in caisson disease, but may be found apart from exposure to increased air pressure. He points out that the disease is usually relatively asymptomatic, and may become evident only after many months and even years, when the heads of long bones, such as the femur or humerus, show compression changes due to absorption. However, he reports 1 case in which severe pain and prolonged invalidism were striking features. In other cases dense shadows, found in the diaphysis and shaft of long bones, were entirely asymptomatic and found only on examination for other causes. In many instances, no infarction could be seen on roentgenographic examination, but microscopic study of autopsy specimens showed definite evidence of such change.

The only lesions requiring treatment are those occurring in the vicinity of a joint since in the diaphysis few symptoms are present and there is gradual development of spontaneous reorganization. In all cases of involvement of the head of the femur, it is necessary to avoid weight-bearing of the affected limb for a matter of two or three years, until there is roentgenographic evidence of reorganization of the necrotic area. When marked deformity, due to necrosis, has taken place in the head of the femur, it is necessary to do an arthroplasty or arthrodesis.

In the author's opinion more thorough studies are necessary to clarify the cause of these vascular occlusions, since systematic autopsy examination of long bones has revealed lesions not observed roentgenographically and routine roentgenographic examination, correlated with autopsy material, showed the presence of many infarcts which were not suspected clinically.—*A. K. Wilson, M.D.*

Harris, Raymond, and Prandoni, Andrew G. Generalized primary lymphangiomas of bone; report of case associated with congenital lymphedema of forearm. *Ann. Int. Med.*, Nov., 1950, *33*, 1302–1313.

The authors point out that an extensive review of the available literature revealed only one previously reported account of primary lymphangioma of bone. They report a case of widespread multiple cavernous lymphangiomas of bone associated with congenital lymphedema of the left forearm.

The patient was a twenty year old white Army private complaining of swelling of his left forearm. This had been present since birth, and he also had a history of "destructive lesions" in ribs and of masses in the axillary region at varying times.

The complete findings of the physical examination are given. Roentgenograms were also made and the following changes were noted: Routine films of the chest revealed cystic lesions of the ribs and examination of the entire skeleton demonstrated generalized cystic lesions involving almost every bone. Differential diagnosis brought up the following entities for most serious consideration: (1) hyperparathyroidism, (2) polyostotic fibrous dysplasia, and (3) multiple hemangiomas. The definite pathologic diagnosis was made from a rib biopsy, the photomicrographs of which are reproduced.

A discussion of the etiology and possible relationships of bone lymphangioma to other conditions giving comparable osseous lesions is presented.

The patient's prognosis was given as poor, and it was felt that new lesions would continue to develop. Radiation therapy is contemplated if the condition becomes more symptomatic. The factor of heredity is important should the patient marry.—*R. D. Moreton, M.D.*

Sussman, Marcy L. Skeletal changes associated with diseases of the blood. *Bull. New York Acad. Med.*, Dec., 1950, *26*, 763–778.

This is the Wesley M. Carpenter Lecture, given on October 12, 1950, before the 23rd Graduate Fortnight of the New York Academy of Medicine.

The author discusses the bone changes in certain diseases of the blood, such as leukemia, myelosclerosis with leukoerythroblastic anemia, familial hemolytic jaundice, sickle-cell anemia, and familial erythroblastic anemia. He advances the theory that the changes in the bones are due to disturbance in the metabolic and enzyme systems, qualitatively and/or quantitatively specific for such disease, which alters the protein substrate available for bone formation and the physicochemical conditions for calcium precipitation.

The accepted assumption that the bone changes in acute leukemia, chloroma and chronic leukemia are due to a mechanical crowding of the marrow space by leukocytic tissue is challenged on the basis of the following discrepancies: (a) there is general agreement that the transverse metaphyseal zone of diminished density is not seen exclusively in leukemias; (b) the skeletal lesions appear and disappear rapidly, the speedy reossification as a result of administration of folic acid antagonists (aminopterin) being especially remarkable; (c) there is lack of response of the associated intrathoracic lesions towards aminopterin; and (d) the use of folic acid antagonists in the treatment of leukemia followed the observation that folic acid seemed to stimulate the leukemic process.

The author considers that folic acid is essential to the normal function of all cells. Rapidly growing immature granulocytes fix or utilize an excessive amount of folic acid creating a relative deficiency of this substance in other metabolic functions. Aminopterin is taken up by rapidly metabolizing leukemic cells in place of folic acid. This makes folic acid

available to correct the deficiency present in other tissues. With continued therapy, the increased leukemic requirements being met by aminopterin are reduced as the number of immature cells is reduced. Part of the freed aminopterin enters into competition in the enzyme systems of normal tissue. The further administration of aminopterin during a clinical and hematologic remission leads to re-appearance of rarefaction in the metaphysis. A diffuse fine fibrosis of the marrow results.

This alteration in the marrow is also found in myelosclerosis but with physicochemical conditions such that excess rather than less calcium is precipitated.

Familial hemolytic jaundice, sickle-cell anemia, and erythroblastic anemia all have one thing in common: they represent a congenital dystrophy of erythropoiesis. The skeletal changes, which vary considerably in incidence, severity, extent and distribution are ordinarily thought to result from the overgrowth of marrow causing dilatation of medullary cavity and pressure atrophy of spongiosa and corticalis. Familial hemolytic jaundice shows the most bone lesions, congenital hemolytic jaundice the least. There is some suggestive evidence that adrenocorticosteroids may have a role in these conditions.

In conclusion, the author suggests that the bone changes in the above described diseases of the blood may, in certain cases, be a secondary tissue reaction based on physicochemical alterations rather than a purely local cellular response to the adjacent disease process.—*Joseph Levitin, M.D.*

Wilner, Daniel. A roentgen study of skeletal and intrathoracic metastases from salivary gland cancer. *Radiology*, Dec., 1950, *55*, 801–806.

This is a study of the incidence of skeletal and intrathoracic metastases from carcinoma of the salivary glands. Of a total of 716 patients, 49 showed evidence of spread to the bones or lungs. It has been generally accepted that such spread is rare but in this series it constituted 6 per cent of the total.

The pulmonary metastases were evidenced by nodules, usually large and similar to sarcomatous metastases, but there were a few patients in whom small nodules were seen.

The osseous metastases were mainly osteolytic with no characteristic distribution or local findings. They are discussed as erosive, patchy and lytic.—*C. A. Stevenson, M.D.*

Hatoff, Alexander. Bipartite navicular bone as a cause of flatfoot. *Am. J. Dis. Child.*, Dec., 1950, *80*, 991–992.

Refractory flatfoot, particularly in children before the age of eight or nine years, is sometimes due to a supernumerary bone. Some of these bones undoubtedly cause symptoms of, or predispose to flatfoot. In some, hypertrophic arthritis develops in the true joint space. Surgical removal is thus often indicated. The author reports a case of flatfoot in an eleven year old white girl who, while jumping from a roof to roof, fell on a fence, sustaining fractured ribs, contusions and subcutaneous emphysema. On the tenth hospital day she complained of pain in the arches of her feet, although these areas were not involved in the injuries. Physical examination revealed evidence of bilateral pes planus. Roentgenograms showed prominence of the tuberosity of the right navicular bone. An accessory navicular bone appeared to be joined to the main body of the right navicular bone. No active treatment was given. The symptoms disappeared spontaneously in a short time.

The author stresses the importance of the fact that the condition is not usually recognized by the physician ordinarily caring for children, particularly those children with refractory flatfoot.—*R. S. Bromer, M.D.*

Swoboda, W. Anguläre dorsolumbale Kyphose als unbekanntes Skelettzeichen beim kongenitalen Myxoedem. (Angular dorsolumbar kyphosis as an unrecognized skeletal sign of congenital myxedema.) *Fortschr. a. d. Geb. d. Röntgenstrahlen ver. m. Röntgenpraxis*, Dec., 1950, *73*, 740–749.

The author studied 7 cases of infantile myxedema all of which had incomplete wedging of the second lumbar vertebra producing angular kyphosis. This or neighboring vertebrae may be affected with variation in degree. The abnormality produced clinically appreciable gibbus in most of the cases. The involved vertebral body has characteristically a step-like wedging anteriorly and superiorly. No follow-up studies could be presented at this time.

In the differential diagnosis of diseases producing kyphosis, dysostosis multiplex, Morquio's disease, and chondrodystrophy must be considered in the infantile group. The author discusses the pathogenesis, feeling that a developmental error producing both the hypothyroidism and bone change exists. The isolated vertebral wedging and resulting kyphosis are described as a previously unrecognized sign of infantile myxedema. Six reproductions of roentgenograms and one sketch of the findings are given. —*L. A. Nash, M.D.*

Coley, Bradley L., Higinbotham, Norman L., and Groesbeck, Harvey P. Primary reticulum-cell sarcoma of bone; summary of 37 cases. *Radiology*, Nov., 1950, *55*, 641–658.

As a basis for this study a total of 37 cases of primary reticulum-cell sarcoma of bone, observed at Memorial Hospital (New York) since 1925, was

considered. A definite, sound set of criteria for inclusion in the series was adopted and applied.

Primary reticulum-cell sarcoma of bone is a malignant tumor histopathologically identical with reticulum-cell sarcoma elsewhere in the body. It arises in a single bone and is capable of regional and distant metastases. It occurs most commonly in males, most often in the third or fourth decades. Typically the course is more benign than that of any other malignant tumor of bone. Lack of debility is noted in most patients. Trauma cannot be established as an irrefutable etiologic factor. Pain is the most significant symptom, being present in all cases on admission. Swelling in the soft tissues contiguous to the tumor occurs in most cases. Fever and local heat are inconstant findings. Pathologic fracture occurred in 8 out of 37 cases.

There are no fully pathognomic roentgen findings in primary reticulum-cell sarcoma. It almost invariably arises in the medullary portion of the bone, presenting a predominantly destructive, osteolytic picture, at times accompanied by less prominent areas of productive changes. The cortex is destroyed without expansion or thickening and some degree of extension into the soft tissues occurs in most cases. Periosteal thickening is never a prominent feature and when present is usually of a thin, lamellated variety. It is not uncommon for the tumor to cross the epiphyseal line. Diseases of bone which may be roentgenologically similar to reticulum-cell sarcoma are: osteogenic sarcoma, Ewing's sarcoma, osteomyelitis, and carcinoma metastasis to bone.

Adequate biopsy is required for diagnosis and should be obtained as early as possible because the prognosis is good in those cases which are adequately treated prior to the occurrence of metastatic foci.

Primary reticulum-cell sarcoma is highly radiosensitive and chances for radiocurability are good. Twenty-seven cases in this series received roentgen therapy. A study of results in these cases leads to the expressed opinion that a calculated tumor dose of at least 3,000 r is optimum for the average case. It does not appear that surgery, either alone or in conjunction with irradiation, offers a sufficiently greater chance of survival to justify amputation. Coley's toxins were given in conjunction with roentgen therapy in most of the authors' cases and the belief is expressed that this is definitely indicated.

End results for this series show 10 cases (out of a total of 24) alive and free from disease after five years and 5 cases (out of a total of 13) alive and free from disease after ten years.—*A. W. Sommer, M.D.*

Blood and Lymph System

LeRoy, George V. Hematology of atomic bomb casualties. *Arch. Int. Med.*, Nov., 1950, *86*, 691–710.

The author, a member of the Joint Commission to Investigate the Effects of the Atomic Bomb in Japan, attempts to simplify a seemingly great mass of detail as applies to the response of the hematopoietic system to ionizing radiation. Source material was the victims, and survivors of Nagasaki and Hiroshima. The project was aided by physicians of the United States Navy and Army plus Japanese doctors. The laboratory procedures were relatively standardized and, with the exception of blood clotting and bleeding times, can be considered valid.

The patients were grouped as to very severe and severe reactors. Those in the first group manifested epilation and purpura, while the latter manifested vomiting or some type of hemorrhagic picture.

A severe leukopenia with a nonspecific depression of the myeloid series was the outstanding finding. This tended to occur almost immediately in the first group. The second group showed this response within three to five weeks. Where recovery occurred, the blood picture returned to normal at about the eighth week. This leukopenia closely corresponded to the peak of the clinical crisis.

The response of the other elements was of no practical importance. The author has done an excellent piece of work, considering the impossible number of variants which must have been present. His figures are in accord with current experimental data.—*F. W. O'Brien, Jr., M.D.*

Moore, George E., and Bridenbaugh, Richard B. Portal venography. *Surgery*, Nov., 1950, *28*, 827–831.

The authors describe a method of injecting contrast medium into the portal vein of the liver to opacify the portal circulation and liver for roentgenographic examination. All venographic examinations have been performed in the operating room as incidental procedures on patients undergoing various surgical operations requiring laparotomy.

A polythene catheter is inserted into one of the tributaries of the portal vein; usually the gastroepiploic vein. After the tip of the catheter is in the portal vein, 20 cc. of 35 per cent diodrast is injected in two or three seconds, and a roentgenographic exposure is made by means of a mobile roentgen machine. A hand-operated Potter-Bucky diaphragm is used. Seventy per cent diodrast is used in those cases in which an attempt is made to visualize the entire liver, because a more concentrated medium is necessary for this type of roentgenogram. Two separate exposures must be made if the portal radicals as well as the entire liver are to be demonstrated.

Good visualization of the portal radicals depends on direct injection of the contrast medium into the portal vein, rapid injection of the contrast medium, complete arrest of respiration during roentgenographic exposure, and proper timing of the exposure in relation to the injection of the contrast medium. The authors have not noted serious untoward reac-

tions. They state that practical applications of the method have not yet been determined.—*C. B. Holman, M.D.*

Leger, L., Gally, L., Arvay, N., Oudot, J., and Auvert, J. La portographie; technique, étude expérimentale, anatomique et clinique. (Portography; technique, experimental, anatomical and clinical study.) *Presse méd.*, March 28, 1951, *59*, 410–411.

Portography includes visualization of the portal system, its tributary vessels and collecting venous trunk. In addition, opacification of the liver may be obtained. The method was first reported by Sousa Pereira who showed latent thrombosis in the cecal veins in chronic appendicitis.

The present authors are interested particularly in the main portal trunk as a means of investigating the surgical treatment of portal hypertension by portal-caval anastomosis. The experimental work was done on large dogs; 10–20 cc. of diodone (50–70 per cent) were injected. In living dogs, only the portal trunk and the liver were visualized. In dead animals, the anatomical relations of the portal trunk tributaries were studied particularly in relation to the vena cava and aorta. A second series of animals was studied in which a ligature stenosis of the portal vein had been established.

Portography was also carried out in human subjects who were subjected to upper abdominal surgery. When the portal circulation was free and rapid, good visualization was not obtained. The liver became opacified rapidly, hiding the details of the intrahepatic branches of the portal vein. However, in the presence of an obstruction, good results were obtained. Details of the injection technique are given.

The authors propose to use the technique in the study of hepatic cirrhosis.—*M. L. Sussman, M.D.*

Kloss, K., and Radlinger, C. Kontrastmittelschäden nach perkutaner Arteriographie. (Harmful effects of contrast material following percutaneous arteriography.) *Wien. klin. Wchnschr.*, Dec. 8, 1950, *62*, 914–917.

The reactions of percutaneous arteriography with 35 per cent diodrast are divided into 2 groups, surgical complications and those due to the contrast material.

Group 1 includes puncture of the esophagus, trachea, or jugular vein and postoperative hematoma. In 130 investigations, there was 1 case of paralysis of the recurrent laryngeal nerve either due to extravasation of the dye or direct injury with the needle. Hematomas may be avoided by digital compression of the artery while withdrawing the needle. A certain amount of precaution and the use of a narrow-gauge needle will reduce the number of serious complications.

In Group 11 belong those reactions attributable to individual sensitivity of the patient to the dye, chemical irritation of the cerebral tissues, and rupture of a diseased, intracranial vessel. In the authors' series, 70 per cent of the patients complained of an intense, unilateral, facial redness, homolateral lacrimation, painful tongue, and excessive perspiration at or soon after the injection. Other reactions included headaches, nausea, and urticaria. Most of these changes are transitory, usually disappearing in a few hours, although the literature contains at least one report in which symptoms lasted six weeks. In the authors' series, a patient, aged sixty-six, complained of left-sided weakness, then complete paralysis of the left side. After twenty hours, spastic hemiplegia and a central facial paresis developed. Almost complete recovery was noted after three months. The paralysis may have been due to vasospasm, ischemia, and edema with or without local hemorrhage. The authors feel that their technique was somewhat faulty, that a small clot may have formed at the site of the injection and started the sequence of events observed.—*Joseph Zausner, M.D.*

Kloss, K. Technik und Wert der zerebralen Arteriographie. (Technique and value of cerebral arteriography.) *Wien. klin. Wchnschr.*, Dec. 25, 1950, *62*, 960–963.

A brief history of arteriography, including method of injection, choice of contrast material, and improvement in roentgenographic procedures, introduces this article. The author divides the arteriographic changes as follows:

A. Changes in the main stem:
   1. Filling defects:
      a. Embolic processes.
      b. Spastic processes.
   2. Changes in caliber:
      a. Increased in hypertension.
      b. Irregular in arteriosclerosis.
      c. Narrowed in edema.
   3. Anomalies:
      a. Localized: traumatic aneurysm.
      b. Regional: congenital aneurysm, angioma.
   4. Displacements: tumor, subdural hematoma.

B. Changes in the branches:
   1. Localized:
      a. Increased number of vessels: glioblastoma, meningioma.
      b. Decreased number of vessels: astrocytoma, oligodendroglioma.
      c. Absence of vessels: abscess, tuberculoma, cholesteatoma.
   2. Generalized:
      a. Increased number of vessels: normal.
      b. Decreased number of vessels: hydrocephalus.

C. Changes in circulation time:

1. Increased: thrombosis, increased intracranial pressure.
2. Decreased: aneurysm.

The diagnoses in 130 arteriographic examinations of 115 patients included: 26 expanding lesions, 19 arterial occlusions, 15 vascular lesions, 6 aneurysms, 2 subdural hematomas, and 47 normals. Of 41 cases clinically diagnosed as expanding lesions, 21 were corroborated by arteriography; in the remaining 20 cases, there were 2 arterial occlusions and 18 normals. Positive roentgenograms were obtained in 3 of 4 epileptics: 1 expanding lesion, 1 vascular lesion, and 1 aneurysm. The ratio of positive to negative findings for the entire series was 68:47.

The technique used is as follows: The patient is given H. E. S. (heptadon, ephedrine, scopolamine) one-half hour prior to arteriography. Novocain (0.5 per cent) is injected superficially into the neck at the level of the thyroid cartilage adjacent to the border of the sternocleidomastoid muscle. After palpating the common carotid artery, the needle is inserted percutaneously so as to enter the vessel at an angle. On obtaining blood in a forceful stream, 10 cc. of diodrast is injected as quickly as possible. The first exposure is made as soon as the syringe is emptied. Physiological saline is infused slowly between injections of contrast material. When the study is completed, the needle is withdrawn slowly and the vessel is digitally compressed for one to two minutes to avoid hematoma.—*Joseph Zausner, M.D.*

Palmer, Thomas H. Aneurysms of the splenic artery. *New England J. Med.*, Dec. 21, 1950, *243*, 989–993.

The diagnosis of aneurysm of the splenic artery is almost always made at the time of abdominal exploration or at postmortem examination. The condition is rarely diagnosed from clinical findings because it is not considered, although its recognition would be desirable since death usually occurs from spontaneous rupture, and operative intervention before rupture could save the life of the patient.

Except for the aorta, the splenic artery is the most common vessel in the abdomen in which aneurysms occur. There are three major causes of aneurysm of the splenic artery: (1) arteriosclerosis, which is most common; (2) mycotic infiltration of the walls from vegetations on the heart valve; and (3) congenital defects in the walls. Occasionally trauma and syphilitic arteritis also play a role in the causation of the lesion.

Splenic artery aneurysms behave like other aneurysms and massive rupture into the abdominal cavity is the most frequent outcome. The aneurysm may rupture into the stomach or colon and occasionally into the retroperitoneal tissues.

Diagnosis before rupture is quite difficult due to the indefinite symptomatology. The pain, when present, may simulate the pain observed in peptic ulcer, cholecystitis or pancreatitis. Vomiting is quite frequent. Small hemorrhages into the stomach or colon may occur resulting in melena and anemia. Physical examination may reveal a mass in the upper left quadrant if the aneurysm is large. Expansile pulsation of the mass is usually present. A bruit may be heard on auscultation. Splenomegaly is common.

Roentgenologic studies may show calcific deposits in the form of round or oval shadows of increased density in the left upper quadrant of the abdomen. There may be a thin line of calcification at the periphery of the aneurysm creating a "cracked eggshell" appearance. The center of the aneurysm is usually at the level of the twelfth dorsal or the first lumbar vertebra. The aneurysm is usually found superior to the upper pole of the left kidney, posterior or posteromedial to the mid portion of the stomach and superior to the splenic flexure of the colon. Cysts of the pancreas may give a similar picture roentgenographically but calcification is quite rare in the cysts.

The symptoms and signs following rupture of an aneurysm of the splenic artery depend on the extent of the rupture. In some cases there is a small hemorrhage which produces epigastric pain, vomiting and tenderness. In others, the hemorrhage is massive, provoking sudden severe pain in the epigastrium radiating toward the left shoulder. Vomiting, tenderness and muscular rigidity of the abdominal wall follow, culminating rapidly in severe shock. If rupture occurs into the stomach, hemetemesis results or copious bright red blood in the stool if it ruptures into the colon. Death results in twenty-four hours if not treated. The diagnosis after rupture may be confused with that of perforated peptic ulcer, ruptured ectopic pregnancy, acute pancreatitis, mesenteric thrombosis, embolism and acute intestinal obstruction.

The treatment consists of surgical removal of the aneurysm. This should be done as soon as the diagnosis is made because of the danger of rupture. The spleen does not necessarily have to be removed if the condition of the patient does not permit it.

The author presents a complete case report illustrating the above findings.—*C. W. Cooley, M.D.*

Pack, George T., and Miller, Theodore R. Hemangiomas; classification, diagnosis and treatment. *Angiology*, Oct., 1950, *1*, 405–426.

A hemangioma as defined by the authors is a tumor or autonomous new growth of tissue in which there is actual formation of vessels or proliferation of vessel walls.

The following classification is given:

Tumors of Blood Vessels

Capillary hemangioma
  Simple type
  Port wine stain (nevus vinosus)

Nevus araneus. Nevus flammeus. De Morgan spots
Sclerosing hemangioma
Infectious hemangioma
Pyogenic granuloma
Granulation cell sarcoma
Cavernous hemangioma
Superficial type
Visceral type
Hypertrophic hemangioma
Simple type
With metaplastic elements
Cirsoid or racemose hemangioma
Arteriovenous fistula
Systematic hemangiomatosis or hemangioma unius lateralis
Congenital
Acquired
Hereditary hemorrhagic telangiectasis (Rendu-Osler-Weber's Disease)
Congenital neurocutaneous syndromes associated with angiomatosis
Von Recklinghausen's neurofibromatosis and angiomas of the skin
Bourneville's syndrome with tuberous sclerosis
Pringle's disease and regional angiomas
Stürge-Weber's disease. Encephalofacial angiomatosis
Lindau-von Hippel's disease. Hemangiomatosis of retina and cerebellum
Hemangiopericytoma
Benign glomus tumor (Masson)
Malignant type (Stout's tumor)
Special regional hemangiomas
Orbit and eye
Brain
Tongue
Gastro-intestinal tract
Liver
Skeletal muscle
Bone
Malignant tumors of blood vessels
Angiosarcoma
Endothelioma
Hemangiopericytoma
Kaposi's idiopathic sarcoma

The hemangioma is the most common tumor of infancy and childhood. Seventy-five per cent of them are present at birth and the greater part of the remainder become recognizable in early infancy. Many are multiple and are more common in females in the ratio of about two to one. They are uncommon in Negroes and over 50 per cent are situated on the head and neck.

The authors point out the main characteristics of each type of angioma, discussing at the same time the special treatment of each type, particularly when the location of the tumor calls for special precautions or procedures. The generally accepted procedures are as follows:

1. *Cryotherapy:* Carbon dioxide snow is the most practical agent and is most satisfactory for superficial hemangiomas which are not too thick. With proper precautions three to ten applications can be given at intervals of two to three weeks. Those in infants respond best to this method. A large tumor may be divided into several smaller areas. The capillary and cavernous hemangiomas are most responsive to this form of therapy if they are not too deep or thick. The port wine stain is usually resistent.

2. *Injection Therapy:* The principle of treatment is the same as for varicose veins. If the intratumoral circulation is sluggish the injection is usually effective. The commonly used chemical sclerotics are injected through a No. 25 gauge needle at intervals of one to four weeks. The racemose (cirsoid), muscle and systemic angiomas usually do not respond well because the swiftly flowing blood disperses the sclerosing solutions before the endothelium can be injured sufficiently to cause thrombosis.

3. *Combined Injection Treatment and Vascular Ligation:* This is necessary for the large racemose and huge systemic hemangiomas. Multiple ligations may be necessary.

4. *Radiation Therapy:* The hemangiomas are more sensitive to irradiation during infancy and early childhood. The authors state that the predictable success of radiation therapy is not an indication for its use. Their objections are the late after results such as skin atrophy, telangiectasia of the facial skin requiring plastic repair, occasional late radiation necrosis in areas which have a poor blood supply, permanent alopecia, interference with bone growth after seemingly small doses over growing epiphyses, and retardation of breast development in females or genital development in males. If there is a lesion near the eye, orbit or eyelid one must be sure that there are no other defects in the eye related to the tumor which may later be attributed to the treatment. The eye cannot be adequately protected if radium is used. Radiation cataracts or secondary glaucoma secondary to radiation iridocyclitis have been reported many times.

Deep seated masses can be treated with gold radon seeds (4 mm. long, filtered with 0.3 mm. Au).

Surface applications of radium can be used, seldom exceeding 1 to 2 skin erythema doses. Repetition may be required in four to ten months. The skin around the tumor is protected. A radon bulb (4 mm. diameter) can be used for its beta-ray effect for tiny punctate hemangiomas.

Primary hemangiomas of bone (especially of the vertebral column) respond well to high voltage roentgen therapy in the absence of spinal cord compressions. The large cavernous hemangiomas of the liver can be obliterated by roentgen therapy.

5. *Surgical Treatment:* Many lesions are so well encapsulated and redundant that surgical excision is the simplest and best method of treatment. Cavernous hemangiomas of the liver may be enucle-

ated if they are encapsulated. In the gastrointestinal tract hemorrhage or obstruction may necessitate surgical intervention. Bleeding or ulcerating lesions of the tongue not suitable for treatment by other means may be resected after external carotid artery ligation.—*Norman Heilbrun, M.D.*

Bowers, R. E. Treatment of haemangiomatous naevi with thorium X. *Brit. M. J.*, Jan. 20, 1951, *1*, 121–124.

In a brief discussion of the natural history of hemangiomas, the author points out that the raised (cavernous) nevi usually resolve spontaneously by the age of five or six. The flat ("port wine") hemangiomas have yielded the most unsatisfactory results in therapy before the advent of thorium X.

All available cases of hemangiomatous nevus were treated with a thorium X-alcohol solution containing 1,500 e.s.u./ml. Thorium X has a half-decay period of 3.64 days, and emits alpha particles which penetrate the surface of the skin 0.2 to 0.3 mm.

The number of paintings with the thorium X-alcohol solution varied from 2 to 109 in the 44 cases reported. Out of these 44 cases, the results were considered good in 20, moderate in 12, and poor in 12. No serious damage attributable to thorium X was seen.

The author concludes that the deep red nevi are difficult to treat, whereas the faint ones are likely to undergo improvement no later than the twelfth painting. The erythema from the previous painting is allowed to subside before the succeeding application is made. The value of pin-point cauterization of residual telangiectases, the use of carbon dioxide snow and cosmetics is also discussed.—*J. D. Reeves, M.D.*

Heycock, J. B., and Dickinson, P. H. Haemangiomata of the intestine. *Brit. M. J.*, March 24, 1951, *1*, 620–621.

This is a report of a patient with gastrointestinal bleeding due to multiple hemangiomas of the intestine. The authors point out that many of these patients have hemangiomas of the skin. The case reported had prolonged gastrointestinal bleeding for three years without evidence of a lesion in the gastrointestinal tract by roentgen examination performed on a number of occasions. The patient was explored, and numerous small hemangiomas were removed from both small and large bowel by excision of the individual lesions.—*E. A. Addington, M.D.*

Thompson, Acors W., and Shafer, June C. Congenital vascular anomalies. *J.A.M.A.*, March 24, 1951, *145*, 869–875.

The authors suggest a simplification of the complex nomenclature now in use to describe the various types of congenital vascular anomalies.

Phlebarteriectasia is a term used to designate a diffuse dilatation of arteries and veins, and phlebectasia is used to designate enlargement of the venous channels over an entire part.

Investigations by Sabin have shown that the blood vessels spread over the developing embryo in definite sheets of capillaries. In these primitive vessels a certain vessel could originally serve as an artery and then be reduced to a capillary plexus or a vessel could serve as a vein and subsequently receive new arterial connections and become an arterial plexus with an entire change in the direction of blood flow. An abnormal development of arteries and veins from the capillary plexus would seem to afford the chief explanation of the occurrence of vascular anomalies.

Most vascular anomalies occur in the vessels of the head and neck or the extremities. Among the deep sites which have also shown involvement are the pulmonary, hepatic and renal vessels. Most are apparent at birth or shortly after although lesions may develop during the first four decades of life. The clinical picture is variable and depends upon the number, size and location of the fistulas.

In an extremity, the lesion may be indicated by unilateral distention of the veins not necessarily tortuous or incompetent.

A pulsating vascular mass may be palpable and exhibit thrills and bruits. The skin temperature may be elevated to as high as 90° F. There may be hypertrichosis and hyperhidrosis. If situated close to an open epiphyseal center, hemihypertrophy may be present. Cutaneous atrophy and chronic ulcerations may occur as late results.

Since the clinical picture is frequently inconclusive, roentgenographic visualization of the vascular structures after arterial or venous injection of a contrast medium is of great diagnostic aid. In arteriography Allen and Camp record three common characteristics: dilation of the arteries leading to the fistula, absence of normal arteries distal to the fistula and pooling of the contrast medium in the region of the fistula.

Congenital anomalies involving venous segments may present the following characteristics: large sinusoidal collections of opaque material, irregularity in the caliber of the veins, and minute clusters of opaque material throughout the involved area.

Other diagnostic procedures described by the authors are: measurement of oxygen saturation of venous blood—an increase being indicative of a fistula; measurement of the localized elevation of skin temperature in arteriovenous lesions; and determination of the venous pressure which shows elevation in arteriovenous fistula, and no change in phlebectasia.

The paper represents an excellent general review of the subject and concludes with a presentation of 10 cases of congenital arteriovenous and venous malformations.—*W. W. Maver, M.D.*

Silver, Henry K. Mediterranean anemia in children of non-Mediterranean ancestry. *Am. J. Dis. Child.*, Nov., 1950, *80*, 767–778.

The author reports a series of cases of Mediterranean anemia in non-Mediterraneans who showed both the major and minor manifestations of the disease. The patients included Chinese, French-Filipino and Mexican children. The disease is found primarily in offspring of families native to areas adjoining the Mediterranean Sea. Other important manifestations of the disease include its familial nature, the presence of "target cells," a blood picture which is hypochromic and microcytic, conspicuous variation in the size of the red cells and increased resistance of the erythrocytes in hypotonic sodium chloride solutions.

A milder form of the disease is characterized by mild or absent anemia, increased reticulocytosis, absence of erythroblastosis and presence of anisocytosis, poikilocytosis, target cells and basophilic stippling of the red cells in the peripheral blood. It has been suggested by Caffey that persons with mild Mediterranean anemia might reach adult life and constitute the source of transmission of the disease. This hypothesis has been confirmed by later writers. At present it is believed that the disease is due to an anomaly of the red blood cell which is inherited as an incomplete recessive or incomplete dominant characteristic. Although Mediterranean anemia was first believed to be a severe childhood disease with a poor prognosis which was seen only in peoples from the Mediterranean area, it is actually a disease of adults as well as of children, manifesting itself through a wide range of clinical severity, with some patients showing severe symptoms, others having a carrier state and still others, displaying mild forms, who have no anemia and a normal life span. All these types are encountered in peoples from various parts of the world.—*R. S. Bromer, M.D.*

General

Switzer, Paul Kent, Moseley, Vince, and Cannon, William Maurice. Extramedullary plasmacytoma involving pharynx, skin and lymph nodes. *Arch. Int. Med.*, Sept., 1950, *86*, 402–411.

A case of a fifty-three year old Negro showing lesions of the skin of the face and body, of the mucous membrane of the pharynx, and enlarged lymph nodes, is presented. The skin lesions were pinkish, non-tender, soft, pedunculated, and easily traumatized; they have increased in size and number spreading from the face to the trunk and extremities.

The clinical picture and histopathologic studies led to a diagnosis of eosinophilic xanthogranuloma. However, chemical studies of blood cholesterol and fat content in tumor led to the diagnosis of extramedullary plasmacytoma.

The lesions did not respond to 1,000 r roentgen treatment, or to nitrogen mustard therapy.—*F. H. Squire, M.D.*

Irvins, John C., Dockerty, Malcolm B., and Ghormley, Ralph K. Fibrosarcoma of the soft tissues of the extremities; a review of seventy-eight cases. *Surgery*, Sept., 1950, *28*, 495–508.

This article is a review of the clinical records and pathologic specimens of 78 cases of fibrosarcoma of the extremities in which treatment had been administered at the Mayo Clinic during a ten year period. All cases in which there was evidence of primary origin of the tumor from an osseous component were excluded in order that no case of fibrosarcoma of bone be included in this series. Also excluded were all cases in which associated destruction of bone occurred, regardless of the cause. The material was studied by means of paraffin sections. Hematoxylin and eosin stains were employed. Certain tissues were treated by other methods to determine the presence of mucus and reticulin. Sixty-nine per cent of these tumors occurred in male patients. The ages of the patients ranged from twelve to seventy-six years. The upper extremity was involved in 28 per cent of cases and the lower extremity in 72 per cent. The knee, elbow and forearm were the commonest sites. In only 1 case was it thought that trauma might possibly have been responsible for malignant change occurring in a benign neoplasm.

The initial complaint in all cases was the presence of a mass or swelling. Enlargement of the mass was usually slow. Only 29 patients complained of any pain and there were no constant constitutional symptoms. The duration of symptoms ranged from as short a time as one week to as long as thirty years. There was roentgenographic evidence of a mass of soft tissue in 55 per cent of the cases. The relative size of the mass, its proximity to the bone or other vital structures and the presence or absence of destructive changes in bone as determined by the roentgenogram proved to be of assistance in determining the surgical procedure to be employed. The presence of edema depended on the amount of local circulatory blockage by the tumor.

These tumors are usually single but may have multicentric origins. They are usually firm but not hard. Cellular fibrosarcomas may be soft and somewhat fluctuant, while the low-grade fibrous tumors may be nearly as hard as bone. The masses are usually round or lobulated and rather sharply delimited from the normal tissue. There is no apparent relationship between the size of the tumor, its pathologic grade or the result of treatment. These

neoplasms tend to metastasize rather early because of extension into the lumens of the blood vessels.

A rather detailed description of the cytology and histology of the tumors is presented. The typical cell is the fibroblast. It may be fusiform or elongated and has been described by the term "spindle cell." Small blood vessels are scattered throughout the tumors and radiating from these vessels is a delicate network of fibrils which furnishes supporting stroma and gives rise to the lobulated appearance. Lymph vessels have not been observed within these tumors. The periphery is usually identified by a sort of capsule owing to the concentric layering of the cells which are somewhat flat but which otherwise do not differ from the cells found elsewhere in the tumor. This is designated as a "compression zone."

The authors have classified these fibrosarcomas into four relative grades of malignancy after the method of Broders based on the histopathologic structure of the neoplasm.

In 63 cases in which detailed follow-up information was available this method of classification had considerable prognostic significance. The five year survival rates of the patients whose conditions were studied are as follows: Grade 1, 57 per cent; Grade 2, 38 per cent; Grade 3, 31 per cent and Grade 4, 20 per cent. Since primary amputation was done in so few instances one cannot determine whether local excision or amputation is the treatment of choice. Roentgen therapy was administered to 83 per cent of those patients who were considered cured and to 80 per cent of those who subsequently died. The over-all survival rate regardless of the pathologic grade of malignancy was 38 per cent.

The authors also present a rather detailed analysis of the pertinent features of each of the four grades of these tumors.—*C. B. Holman, M.D.*

Cade, Stanford. Soft tissue tumors; their natural history and treatment. *Proc. Roy. Soc. Med.*, Jan., 1951, *44*, 19–36.

A series of 153 patients, the largest yet recorded from a single source, suffering from soft tissue sarcoma is discussed. References to the literature show the rarity of such tumors, the vagueness of the nomenclature and the disappointing results of treatment. Of the 153 patients only 7 have no histopathological confirmation of the diagnosis. In 146 sections and histopathological reports are available; 148 patients have been followed up either to death or to date.

The author defines soft tissue sarcoma as a tumor of mesenchymal origin arising in association with the connective tissue of the fasciae, aponeurosis, tendon sheaths, intermuscular septa, voluntary muscles and synovial membrane. Histopathologically they are classified as:

	Cases
Spindle cell sarcoma	42
Fibrosarcoma	48
Myxosarcoma	11
Synovioma	11
Liposarcoma	7
Neurogenic sarcoma	9
Rhabdomyosarcoma	7
Various	11
No histology	7

The term spindle cell sarcoma should not be used to describe a tumor entity as by "using such a term the reporter confesses his inability to recognize the nature of the tumor." The author also condemns the use of the term "neurogenic sarcoma" to describe a soft tissue sarcoma unless it is derived from peripheral nerves. The 9 cases of neurogenic sarcoma in the author's list had no definite diagnostic features in the sections except for the arrangement of fibers in "whorls." Again the term myxosarcoma is misleading as such a tumor, chiefly composed of fibroblasts with areas of mucoid degeneration, is not a definite clinical entity.

The greatest incidence is between twenty and thirty years of age, but they may occur in infants a few weeks old, in whom fortunately the prognosis is not always hopeless.

The sex incidence shows a preponderance in men for tumors in the trunk and limbs. In other sites the sex incidence is equal. The site incidence shows that the majority occur in the limbs, the lower limb being the commonest site of all. Prognosis is most favorable for tumors in limbs and trunk.

Fibrosarcoma (the commonest type) is derived from fibroblasts. It is composed of spindle cells with an elongated nucleus. Metastases are multiple and widespread. Synovial sarcoma has a distinct histopathology. It occurs in connection with bursae, tendon sheaths or joints. Its prognosis is worse than that of fibrosarcoma.

Liposarcoma is rare. Main features are foamy embryonal fat cells, rapidity of growth and great size.

Rhabdomyosarcoma may be of two varieties—cells with longitudinal and cross striation, and broad ribbon cells.

The term "angiosarcoma" is a descriptive one, designating markedly vascular tumors. It does not imply histogenesis of the cell type.

Three main methods of treatment were used: (1) Wide excision in association with radiation therapy, both pre- and postoperative; (2) Amputation, alone or with irradiation; (3) Irradiation only. Local excision by enucleation proved to be a failure owing to recurrence. Knowledge of the histopathological type is important for prognosis. Amputation is not a "cure." Neither should irradiation alone be advised where wide excision is possible. Irradiation

is of considerable value in the treatment of soft tissue sarcoma, and is an important modality in the treatment of this disease. The results of a combined radiological and surgical approach to this disease are better than surgery alone, however extensive the surgery.

In this series survival up to twenty-six years has been obtained and half the patients have been salvaged. The commonest soft tissue sarcoma, fibrosarcoma, offers the most hopeful outlook. Fibrosarcoma should be given less and not more radiation, and the time factor must be greatly prolonged.

The author suggests that irradiation with moderate doses over long periods breaks the chromosomes, thus causing gene mutations and in time the cells become non-reproductive. Sublethal irradiation may also produce chemical intracellular changes resulting in sterility of the malignant cells.

The author's results showed a longer survival after conservative excision and irradiation than after amputation.—*D. R. Bernhardt, M.D.*

RADIATION THERAPY

Tice, G. M., and Irving, N. W. Roentgen therapy supplementing surgery in the treatment of gliomas. *J. Neurosurg.*, Nov., 1950, *7*, 509–520.

Tice and Irving survey 52 patients with proved brain tumors who were treated by roentgen therapy at the University of Kansas Medical School Hospital. Most patients were treated with 200 kv., corresponding to a half-value layer of 0.9 mm. copper. A few were treated with 250 kv., and half-value layer of 1.7 mm. copper. At the present time they deliver a tumor dose of 5,000 r in one series, or 6,000 r in two series spaced two months apart. In a child the dose is reduced to 4,000 r. However, their living patients have received an average tumor dose of 5,900 r.

Of the 52 patients, 15 are living and 37 are dead. The astroblastoma group shows an average survival rate of 46.4 months with 30 per cent alive for five years. The cellular meningioma and hemangioblastoma group is small; 1 out of 5 patients is alive after five years. The glioblastoma, spongioblastoma, and oligodendroglioma group shows no five year cures, the average survival being sixteen months. Sixteen cases are in the medulloblastoma group, with 21.3 months average survival, none living for five years.—*A. A. Brewer, M.D.*

Friedman, Milton, and Hall, John W. Radiation-induced squamous-cell metaplasia and hyperplasia of the normal mucous glands of the oral cavity. *Radiology*, Dec., 1950, *55*, 848–851.

Irradiation of the normal mucous glands of the oral cavity during roentgen therapy for squamous cell carcinoma of the mouth and oropharynx produced squamous metaplasia of the glandular epithelium in 23 out of 40 patients from each of which a biopsy specimen was studied prior to initiation of therapy.

The time sequence of metaplasia varied widely, generally being most extensive by the fifth or sixth week. It was observed in the ducts as well as the acini and with almost equal frequency.

The sequence of histopathological changes is discussed and the question whether these changes are due to an existing inflammatory condition or entirely the result of irradiation is considered.

In the authors' opinion the process is not precancerous.

Four good figures are presented of a case showing the histopathological change from normal mucous glands to an extensive squamous cell metaplasia.—*E. E. Seedorf, M.D.*

Kander, H. S., and Sicher, K. Treatment of deafness and recurrent otitis media with x rays. *Lancet*, Dec. 2, 1950, *2*, 672–675.

Three years ago, the authors, stimulated by the results of Crowe, Fowler and others in the United States, began treating the lymphoid tissue of the nasopharynx by means of roentgen rays. They believe that these rays are as efficacious as the radium and radon applications used by many.

The selection of cases is very important, if disappointments are to be avoided. Their two main groups were children suffering from deafness, and those suffering from recurrent attacks of otitis media. All the children had had previous tonsillectomies and adenoidectomies. In all, excessive lymphoid tissue was still present in the nasopharynx. Usually the tympanic membrane was retracted and thickened. All patients had audiometric studies.

The technique used was: 200 kv., 50 cm. focus-skin distance, with a half-value layer of 2 mm. Cu. The fields were 8 by 6 or 6 by 4 cm. in size, using two lateral fields to both sides of the face. The centering point was, on the average, 2 cm. in front of the external auditory meatus. The treatments were given on five successive days for a total dose to the eustachian tubes of 1,000 r.

Forty-one cases were so treated and the results as to improvement in hearing and in the number of colds and attacks of otitis media were encouraging.—*R. A. Hays, M.D.*

Ennuyer, A., Calle, R., and Bertoluzzi, M. L'amélioration de la "sécheresse" post-radiothérapique des voies aéro-digestives supérieures par un parasympathomimétique de synthèse: le 2249 F. (Improvement in the

post-radiotherapeutic dryness of the upper aero-digestive tract with the use of a synthetic parasympathomimetic [2249 F].) *Presse méd.*, Dec. 30, 1950, *58*, 1503–1504.

The authors use a drug known as "2249 F" (iodomethylate of dimethylamino-1-methylene-dioxy-2-3-propane) for relief of dryness of the mouth, difficulty in swallowing, and difficulty of expectoration, due to irradiation of the head and neck, and found it to be superior to other preparations, such as pilocarpine, eserine, acetylcholine, and the propandiol acetals. Superiority of this drug, which was discovered by Fourneau, Bovet and Montezin, in 1944, is due to the fact that it can be given in tablet form, it is not stored in the tissues, and does not cause sensitivity.

The drug is put up in 5.0 cg. tablets and, for subcutaneous injection, in 2.0 cg. ampules, each containing 5 milligrams of drug. On the first day, one-fourth tablet is given after breakfast, and one-half tablet is given after each of the noon and evening meals. On the following days each dose is increased by one-fourth tablet daily, until an optimum dose, usually four to five tablets per day, is reached. If disagreeable side effects, such as excessive perspiration, vertigo, etc., develop, the dose is reduced to a point where these are no longer troublesome.

The preparation was used in 23 patients, who had tumor doses ranging from 4,500 to 7,500 r, over periods of time, ranging from 48 to 102 days. Results were excellent in 8 cases, satisfactory in 8, mediocre in 2, and there was no effect in 5. There appears to be no relationship between the effect of the drug and factors such as tumor dosage, interval between completion of treatment, and institution of administration of "2249 F," location of tumor, or dose of the drug. One patient showed no improvement when given two tablets daily, but was markedly improved when given five; other patients achieved satisfactory results with considerably smaller dosage.

In addition to relief of disagreeable symptoms, according to the authors' opinion the drug is useful because production of abundant salivation favors digestive absorption, and may avoid some necrotic complications which would otherwise result from lack of moisture of the buccopharyngeal mucous membrane.—*A. K. Wilson, M.D.*

Kramer, Simon. The treatment of malignant tumours of the nasopharynx. *Proc. Roy. Soc. Med.*, Nov., 1950, *43*, 867–874.

This paper is based on a series of 54 cases of malignant tumors of the nasopharynx treated at the Middlesex Hospital between 1935 and 1949.

Incidence: The Registrar-General's figures for 1948 showed 55 deaths due to cancer of the nasopharynx, an incidence of 7 per 10,000 deaths due to cancer. In the author's series 39 per cent of the patients were under forty-five years of age. The age incidence varied from less than ten to seventy-one years. Men outnumbered women 2:1.

Diagnosis: The initial symptoms may be classified under three headings.

1. Symptoms due to the presence of tumor in the nasopharynx. These are rhino-otological complaints, such as epistaxis, nasal obstruction, and deafness; 27 per cent of the author's cases had rhino-otological symptoms as a first complaint.

2. Symptoms due to extension of the growth beyond the confines of the nasopharynx. These tumors show a strong tendency to invade the base of the skull. This occurs via the foramen lacerum or occasionally through the body of the sphenoid. Once inside the skull, the tumor spreads extradurally along the base of the brain, causing paresis or paralysis of the cranial nerves in the middle fossa. The most common neurological symptom is double vision due to involvement of the sixth nerve. The fifth nerve is commonly affected producing pain and paresthesia in its distribution. Less frequently complete external ophtalmoplegia due to involvement of the third and fourth nerves is seen. Rarely, pressure on the opthalmic veins may cause papilledema. The ninth, tenth, eleventh and twelfth nerves are occasionally affected by intracranial spread or extracranially in the region of the jugular foramen. Nerve palsies may cause mistaken diagnosis of cerebral tumor, especially in cases where papilledema is present. Twenty-four per cent of the patients first complained of symptoms of cranial nerve involvement.

3. Enlarged cervical lymph nodes. In the author's series almost 50 per cent first complained of enlarged cervical lymph nodes, and in 76 per cent enlarged lymph nodes were detected at first examination. They were bilateral in 30 per cent of the whole group.

Roentgenograms of the nasopharynx and lateral laminagrams aid in the diagnosis by revealing a soft tissue shadow in the nasopharyngeal air space. Rarely, gross bony destruction may be seen in a lateral roentgenogram. Erosion at the base of the skull can be better detected in the submento-vertical view. Intracranial invasion may occur without evidence of bony erosion.

Pathology: Biopsy should be performed before treatment. Some growths are so radiosensitive that histopathological recognition may be very difficult if the biopsy is made after appreciable therapy. In this series biopsies were performed in 52 of the 54 cases; 47 cases were positive, while no definite tumor was found in 5.

The author's histopathological classification of tumor cell type is correlated with the normal structures present. Basically, two types of epithelium are found in the nasopharynx; pseudostratified columnar epithelium and squamous epithelium. The squamous epithelium overlying lymphoid tissue is classed as lympho-epithelium. There are numerous mucous

glands and much lymphoid tissue. Malignant tumors can arise in any of these tissues.

In this series there were 42 cases of carcinoma and 5 cases of connective tissue tumor. Lympho-epithelioma, undifferentiated carcinoma, and most sarcomas bear clinical resemblance to each other in growth behavior, lymph node involvement, and response to irradiation. Keratinizing squamous cell carcinoma is moderately radiosensitive. Transitional cell carcinoma usually responds well to radiation therapy, but has a strong tendency to local recurrence.

Treatment: All but 2 cases were given deep roentgen therapy. In the radiosensitive group, where cervical metastases were the rule, an area from the base of the skull to the clavicle was irradiated en bloc by two large lateral fields. The tumor dose given was 3,000–3,500 r in four to five weeks. The general reaction was usually marked, and careful nursing was most important. Complete regression of the primary lesion and of the enlarged cervical lymph nodes could often be achieved by this method. If further treatment was necessary, small fields were used.

In the second group, those with more highly differentiated growths, when no lymph nodes were palpable in the neck, intensive treatment was given the tumor by small beam-directed fields. The tumor dose in these cases was 5,500–6,000 r in six to seven weeks. When lymph nodes were palpable, regional irradiation with large fields was carried out, up to a tumor dose of 2,000 r in two to three weeks. Treatment was then continued with small fields to the primary tumor and the cervical lymph nodes. A tumor dose of 5,500–6,000 r in six to seven weeks could usually be achieved.

The factors employed were 200–250 kv., 10 ma., fore-filter to give a half-value layer of 2.4 or 1.4 mm. Cu, focus-skin distance 40 cm. and 60 cm.

Results: In this series 31 were given radical therapy five or more years ago; 8 cases (25.8 per cent) survived five or more years without evidence of cancer. A high percentage of the deaths occurred during the first two years. Histopathologically, the lympho-epithelioma and undifferentiated carcinoma showed the best five year results. The differentiated squamous cell carcinomas did badly, and the transitional cell carcinomas showed the poorest results. The survival rate is slightly higher (33 per cent as against 25 per cent) in cases where no cervical lymph nodes were palpable. Invasion of the skull carries a bad prognosis. Twenty-one cases showed local recurrence: 18 in the first year and the remaining 3 in the second year.—*D. R. Bernhardt, M.D.*

Frantz, Charles H. Extreme retardation of epiphyseal growth from roentgen irradiation; a case study. *Radiology*, Nov., 1950, *55*, 720–724.

Bone growth in the young can be retarded or stopped by large doses of roentgen rays. Careful measurements of long bones following exposure reveal not only less length than normal but decrease in shaft diameter and cortical thickness. The changes noted in hyaline joint cartilage are apparently insignificant from a clinical standpoint.

The author presents a case report of a sixteen year old white male who now has a shortening of $9\frac{3}{4}$ inches of his right lower extremity. This followed roentgen irradiation to the right thigh and leg for a hemangioma hypertrophicum. This course of therapy was begun when the patient was three weeks of age. A total of 2,400 r (in air) was administered over a period of five months. The excessive shortening through the years serves to warn of the dangers of irradiation in infants.—*E. M. Cooper, M.D.*

Collins, Vincent P. Tissue dose in irradiation of the breast. *Radiology*, Dec., 1950, *55*, 814–818.

The difficulties in comparing results and tissue doses in irradiation of carcinoma of the breast are discussed.

The author describes the use of water-filled rubber balloons enclosed by a special plastic box used as bolus material to build up a field of uniform density about the breast.

By actual measurement he produced isodose curves designating the intensity of irradiation to any portion of the breast when given through two opposing lateral fields.

This method of surrounding the breast with bolus material results in more uniform irradiation and increases the tissue dose delivered.—*E. E. Seedorf, M.D.*

Portmann, U. V. Treatment of cancer of the breast. *Radiology*, Dec., 1950, *55*, 819–826.

The choice of satisfactory treatment of cancer of the breast depends upon the proper diagnosis and classification of the disease.

The following classification based on both clinical and pathologic manifestations was developed in 1937 for an analysis of the series of cases at the Cleveland Clinic.

Group or Stage I

Skin: Not involved.
Tumor: Localized in breast and movable.
Metastases: None in axillary nodes or elsewhere.

Group or Stage II

Skin: Not involved.
Tumor: Localized in breast and movable.
Metastases: Few axillary nodes involved; no metastases elsewhere.

Group or Stage III

Skin: Edematous: brawny red induration or inflammation not obviously due to infection; extensive ulceration; multiple secondary nodules.

Tumor: Diffusely infiltrating breast; fixation of tumor or breasts to chest wall; edema of breast; secondary tumors.

Metastases: Many axillary nodes involved or fixed. No clinical or roentgenologic evidences of remote metastases.

Group or Stage IV

Skin: As in any other group or stage.

Tumor: As in any other group or stage.

Metastases: Axillary and supraclavicular nodes extensively involved. Clinical or roentgenologic evidences of remote metastases.

The author gives the percentage of patients that were classified within each group and he elaborates upon the survival rate of each group with and without postoperative roentgen therapy.

Postoperative roentgen therapy is particularly indicated for patients in Groups II and III in which the five year survival rate is increased approximately 10 to 15 per cent.

The technique of irradiation procedures is not discussed in this paper.

The following "criteria of incurability" are particularly helpful in the choice of treatment of patients within Group III and IV.

The Skin

1. Edema (orange or pigskin) of more than slight extent.
2. Ulceration of more than slight extent.
3. Brawny red and inflamed, not obviously due to infection.

The Breast

1. Diffusely edematous.
2. Diffusely infiltrated.
3. Secondary tumors.
4. Fixation of tumor or breast to chest wall.

Metastases

1. Axillary lymph nodes numerous, extensively involved and fixed.
2. Supraclavicular lymph nodes or edema of the arm.
3. Involvement of contralateral breast or lymph nodes.
4. Remote metastases in bones, lungs, or other viscera.

Patients with more than one indication listed in the "criteria" are not benefited by surgery and should be treated by irradiation procedures alone.—*E. E. Seedorf, M.D.*

Stoll, Basil A. Hormone therapy in relation to radiotherapy in the treatment of advanced carcinoma of the breast. *Proc. Roy. Soc. Med.*, Nov., 1950, *43*, 875–882.

The breast is known to be influenced by secretions of the pituitary, ovary and adrenal glands, and possibly by the thyroid and thymus glands. The complexity of its hormonal relationships poses a great difficulty in modifying hormonal control of this organ.

Increased blood levels of estrogens, induced by gonadal overactivity or therapeutic administration, and androgen administration will depress production of gonadotrophin by the pituitary. These changes are usually temporary. A disturbance of the balance between the secretion of androgens and estrogens in the normal female may possibly predispose to the development of breast malignancy. The disappearance of estrogenic hormones after the menopause exerts an adverse effect on carcinoma of the breast. This is possibly associated with oversecretion of the pituitary gonadotrophin. Both androgens and estrogens are of proved value in postmenopausal cases of breast carcinoma, possibly by suppression of the pituitary oversecretion.

Pituitary oversecretion cannot be so easily incriminated in younger women. In a proportion of premenopausal cases of carcinoma of the breast castration depresses estrogen production and results in clinical improvement. Conversely, estrogen administration may activate a tumor. The safest method of treatment in young women with breast cancer is testosterone administration because it antagonizes both pituitary gonadotrophin and estrogen substances.

After cessation of menses it takes up to three years for estrogens to disappear from the blood and urine of the majority of women. It is therefore considered inadvisable to prescribe estrogens within five years of the menopause.

In a group of 86 women treated with stilbestrol alone, 55 per cent showed regression of lesions, 29 per cent showed progression of the tumor, and 16 per cent remained static. In women over sixty years, 59 per cent showed regression and in those under sixty years, 44 per cent showed regression. A high proportion of cases of women under sixty showing progression of the tumor suggests that it is dangerous to use estrogens for menopausal symptoms in patients with quiescent cancer of the breast. The cases with longer histories (and presumably slow-growing neoplasms) showed a higher percentage of regression. Patients receiving 1–2 mg. daily and those receiving 20 mg. daily showed similar results.

Generally it was noted that the primary tumor responded most markedly, secondary skin nodules a little less, and glandular metastases least of all. Sometimes nodules regressed in one part and spread in another. Nodules of longer standing regressed before more recent ones. In cases of soft tissue regression, the neoplasm often became active again

in one to two years and distant metastases developed despite estrogen administration. Estrogen administration did not relieve the pain of bone metastases or cause recalcification of these lesions. Estrogen therapy appears of good palliative value in cases of pulmonary and pleural metastases. The significant complications of estrogen administration were uterine bleeding (35 per cent) and nausea and vomiting (16 per cent).

Androgen therapy in this series was used only for soft tissue metastases and not for metastatic dissemination to bone. In 26 cases of primary breast cancer and metastatic lymph nodes (treated by irradiation) testosterone was tried for rapidly growing metastatic nodules not easily controlled by irradiation. Of the 26 cases, 39 per cent showed regression, 46 per cent showed progression of the disease, and 15 per cent remained static. Testosterone was given as subcutaneous tablet implants (100–200 mg.) or 100 mg. testosterone propionate intramuscularly semiweekly.—*D. R. Bernhardt, M.D.*

Robnett, A. H., Jones, Thomas E., and Hazard, John B. Carcinoma of the breast; recurrence and survival in 203 patients. *Cancer*, Sept., 1950, *3*, 757–772.

An excellent statistical analysis of 203 cases of carcinoma of the breast is presented. The most important prognostic determinant, omitting remote metastasis, is the extent of lymph node involvement. Cutaneous involvement, the degree of local fixation of the tumor to the chest wall and the histopathologic type are other prognostic determinants.

Portmann's classification is a combined clinicopathologic one and is used in the author's analysis. The over-all five, seven and ten year minimal survival rates are 47.7 per cent, 32.9 per cent, and 26.7 per cent respectively. Breaking this down further, for Portmann Group I cases a 91.7 per cent five year survival rate was noted; for Group II cases, 60.7 per cent five year survival rate; and for Group III cases, 16.1 per cent five year survival rate. It is noted that the five year survival rate in Group II in patients receiving postoperative roentgen therapy was 32 per cent greater than those treated with surgery alone. Group III results for postoperative roentgen therapy are less conclusive.

Local recurrence occurred in about 20 per cent of the cases studied. Postoperative irradiation did not affect the time of appearance of the local recurrence nor did it affect the survival time. Local recurrence apparently corresponds to the degree of involvement of lymph nodes.—*J. G. Lorman, M.D.*

Kaplan, Ira I. The question of genetic injury following x-ray irradiation of the ovaries in the treatment of sterility. *J. Obst. & Gynaec. Brit. Emp.*, Oct., 1950, *57*, 767–779.

It has been ascertained experimentally that certain effects of irradiation upon the reproductive organs of some insects can be observed in their successive generations. But nowhere is there justification in extrapolating such effects to human beings. One case presented is that of a thirty-two year old man who received intensive roentgen therapy for a testicular tumor. Irradiation was directed to the scrotum, inguinal, pelvic as well as epigastric regions. Seven months later azoospermia was demonstrated. Following hormone therapy this status was relieved. The semen was found to be normal. The patient subsequently impregnated his wife, and a child was born, apparently perfectly normal mentally and physically.

It is stated that experience with roentgen treatment of 413 married women for sterility or amenorrhea over a period of twenty-five years proves that when properly administered no deleterious effects result, neither in mother nor offspring, nor on the subsequent children of these offspring.

That roentgen rays were useful in the treatment of amenorrhea and sterility was noted many years ago. But there is still no uniformity of opinion as to the action of roentgen rays. It is not clear whether this is essentially on the pituitary or the ovary or both. Cases are cited as examples of the effect of irradiation upon each individually. When administered over the ovaries, the roentgen rays, it is conjectured, may stimulate the absorption of a persistent corpus luteum, or cause the rupture of mature ovarian cystic follicles with subsequent return to normal menstrual function.

Cases are presented demonstrating that irradiation administered to young virgins for amenorrhea or for abnormal pubertal bleeding does not adversely affect the ability of the young women to have normal children following marriage after such treatment.

The irradiation is carried out with the following factors: 200 kv., 0.5 mm. Cu plus 1 mm. Al filter, at 50 cm. distance through 8 by 10–10 by 15 cm. fields for the ovaries and a 6 by 8 cm. or a 5 cm. round field for the pituitary area. A dose of 50 r in air is given to each anterior ovarian field and 75 r to the anterior pituitary field for the first exposure. One week later, 75 r is given to each posterior ovarian field and 75 r to the anterior pituitary field for the second exposure. Again one week later, 50 r is given to each anterior ovarian field and 75 r to the anterior pituitary field for the third exposure. This completes the series. A fourth exposure is administered only in rare instances.—*H. H. Galston, M.D.*

Brunschwig, Alexander, and Pierce, Virginia K. Partial and complete pelvic exenteration; a progress report based upon the first 100 operations. *Cancer*, Nov., 1950, *3*, 972–974.

All of the patients presented in this report of the first 100 patients who have undergone "ultraradical" surgery had advanced pelvic cancer involving the bladder, rectum, and vagina-uterus or any combina-

tion of the three. In all patients irradiation and/or surgery had failed to control the disease.

A 20 per cent immediate surgical mortality is reported. Eleven of the 20 patients died with urinary tract difficulty. Forty-nine of the patients were classed as short term survivors, i.e., they lived more than one month but less than eight months. Thus there were 69 per cent failures in the entire series.

Effective palliation was achieved in 9 patients, i.e., they survived a year or more and returned to fairly or practically normal activity. They either succumbed to metastasis or are living with evidence of metastasis. An additional 12 patients are called long-term survivors and have lived at least one year and five months, have no evidence of recurrences and have returned to normal activity. There is, therefore, a 21 per cent effective palliation rate when one adds the above two groups. An additional 10 patients have not lived long enough to be classed in any of the above groups.

The authors conclude that ultraradical surgery has something to offer the patient with advanced pelvic cancer.—*J. G. Lorman, M.D.*

Gross, Robert E., and Neuhauser, Edward B. D. Treatment of mixed tumors of the kidney in childhood. *Pediatrics*, Dec., 1950, *6*, 843–852.

This article is a summary of the authors' experiences and results in the treatment of the embryoma or Wilms' tumor in childhood. Their first plea is for revision of the hopeless attitude which has been adopted when dealing with this condition. The gross and microscopic findings are discussed together with the physical findings. An intravenous pyelogram is recommended to determine the presence and function of the opposite kidney, as well as to outline the size of the primary lesion. Kidneys affected with embryomas rarely fail to excrete dye and usually show pelvic distortion as well as displacement. The lungs and bones should be surveyed for metastases.

In evaluating treatment results, all cases encountered should be considered in statistical studies, regardless of operability. Treatment methods include surgery, irradiation, combinations of both, and chemotherapy. The authors dismiss the latter method as being valueless in this condition at this time. A summary is given of some of the more impressive treatment results as found in the literature.

The authors have analyzed a series of 96 cases from the records of The Children's Hospital in Boston, according to three time periods. In the earlier days the surgery was haphazard and the results poor. In the period 1931–1939 the surgery was perfected and the survivals increased from 14.9 to 32.2 per cent. In the period 1940–1947 postoperative irradiation in adequate amounts has been added to the same surgical technique and the survivals rose to 47.3 per cent. The irradiation technique is to begin treatment immediately postoperatively and give 200 r daily, using three alternate portals, anterior, lateral and posterior. A total of 4,000–5,000 r (in air) is given over the tumor bed.

The value of preoperative irradiation has not been established in the minds of the authors and they have abandoned this for immediate surgery following four fatalities in succession, in whom this was tried. They do not believe that irradiation to the chest as a prophylactic measure is sound. Postoperative irradiation to the tumor bed where known tumor material was left at operation has in some cases resulted in apparent cures. This type of case should have repeated intensive series of treatments. If there are widespread lung metastases roentgen therapy should be employed until evidence of extension is apparent.

The authors have noted a definite distinction in the prognosis in the age group under twelve months. In their series from 1940–1947 this group had an 80 per cent survival rate as opposed to the over-all rate of 47 per cent. They feel that any patient surviving eighteen months after treatment without evidence of disease is probably a permanent cure.—*R. M. Harvey, M.D.*

RADIOISOTOPES

Marinelli, L. D., and Hill, Ruth F. Radiation dosimetry in the treatment of functional thyroid carcinoma with I^{131}. *Radiology*, Oct., 1950, *55*, 494–502.

The total beta radiation dose from I^{131} in equivalent roentgens equals 18 times the product of the initial tumor concentration expressed in millicuries per kilogram and the effective half-life in days, provided that there is uniform distribution within the tumor, that the localization time is short compared to the half-life, and that the effective decay curve is exponential. Since the first of these conditions seldom occurs, the formula at best is only a guide. The effective half-life is obtained by determining the decay rate over the tumor by means of a Geiger-Müller counter in constant position and the initial concentration is best determined by biopsy and extrapolation to the time of administration by means of the decay rate curve. It follows, then, that tracer studies are necessary but not too accurate.

The possibility of concentration of I^{131} in other organs and the total body irradiation must be considered. Available reports indicate I^{131} concentration throughout the body follows closely that of the blood except for the stomach juices, saliva, urine, and thyroid. By determinations of blood concentrations of I^{131} on several successive days and by conservative calculations to include both complete decay and gamma radiation, the total body irradiation at infinity in equivalent roentgens per 100 millicuries administered (specific radiation dose) was determined. The ratio between the extremes of specific radiation doses determined on 20 patients showed a ratio of 8.1 to 1 and tracer studies do not

predict too closely the I^{131} content of the blood after intensive therapy. Higher specific radiation doses than expected were obtained from tracer studies. Also, on considering some of the specific radiation doses obtained, cessation of menstruation in females under therapeutic dosage is possible without postulating specific concentration within the ovaries.

The specific radiation doses calculated for the urinary tract and upper alimentary tract show extremely wide variations and the difference between oral and intravenous administration of I^{131} is not significant when considering the total irradiation to the upper alimentary tract.—*M. B. Goodwin, M.D.*

Beidleman, Barkley. Toxic goiter complicating diabetes mellitus treated with radioactive iodine (I^{131}). *J.A.M.A.*, Nov. 11, 1950, *144*, 925–927.

Thyrotoxicosis can activate potential diabetes mellitus and intensify pre-existing diabetes mellitus by increasing the metabolic rate, reducing the secretion and efficiency of insulin, depleting the liver of glycogen, reducing the renal threshold for glucose and increasing the rate of absorption of glucose from the gastrointestinal tract. The treatment of thyrotoxicosis with a variety of methods such as iodine, thiouracil, 6 propyl-2-thiouracil, external irradiation to the thyroid or thyroidectomy has been shown to increase the stability of the blood sugar level and to decrease the insulin requirements in most cases. Radioiodine might be expected to duplicate these results. It has been shown, however, that the liver collects appreciable amounts of radioiodine and the pancreas slight to insignificant amounts of it. Whether the usual therapeutic dose of radioiodine is retained in these organs long enough to affect their antidiabetic functions is unknown, since no patients with thyrotoxicosis and coexisting diabetes mellitus so treated has been reported.

The author reports a patient with a diffuse toxic goiter complicating diabetes mellitus treated with radioactive iodine (I^{131}). In this patient the insulin requirement and the lack of diabetic control were directly proportional to the basal metabolic rate under various conditions. The thyrotoxicosis was successfully treated by radioactive iodine but the insulin requirement was not reduced below that of the prethyrotoxicotic level. Whether this was due to the effects of radioactivity on the liver and pancreas is not known.—*F. J. Rigos, M.D.*

Freedberg, A. S., Ureles, A. L., Lesses, M. F., and Gargill, S. L. Pulmonary metastatic lesion successfully treated with radioactive iodine; report of a case of pulmonary metastasis from a papillary adenocarcinoma of the thyroid. *J.A.M.A.*, Sept. 2, 1950, *144*, 16–19.

The authors report a patient who had a solitary lung metastasis one year after right hemithyroidectomy. Tissue removed at thyroidectomy revealed a papillary adenocarcinoma. The lung lesion disappeared two months after radioactive iodine therapy. A total of 78 millicuries of I^{131} was employed. The uptake of the area of metastasis was originally four times that of an uninvolved control area. At the end of two months after the first therapeutic dose, there was no evidence of localization or concentration of subsequent therapeutic doses of radioactive iodine within the body. Desiccated thyroid therapy was administered to offset symptoms, signs and laboratory evidence of myxedema. Twelve months after the pulmonary metastasis was found, there was no evidence of metastatic recurrence in the lungs or skeleton and the patient was regarded as entirely well clinically. The basal metabolic rate was minus 17 per cent and the serum cholesterol was 238 mg. per 100 cc.

The bibliography refers to similar work done by others since 1942.—*John Turner, M.D.*

Diamond, Henry D., Craver, Lloyd F., Woodard, Helen Q., and Parks, George H. Radioactive phosphorus. I. In the treatment of lymphatic leukemia. *Cancer*, Sept., 1950, *3*, 779–788.

This paper deals with nine years of experience at Memorial Hospital in the palliative treatment of 71 cases of lymphatic leukemia with P^{32}. Fifty-three cases were classed as chronic and 18 as acute. No patients, irrespective of the extent of disease in lymph nodes, spleen, or liver, were denied P^{32} if the bone marrow was neither severely hypoplastic nor bordering on aplastic, and so long as a marked peripheral subleukemia (leukopenic) blood picture did not exist. Only 10 of the chronic and 9 of the acute cases were treated solely with P^{32}. All other cases received P^{32} in combination with roentgen therapy, folic acid antagonists, nitrogen mustards, potassium arsenite and urethane.

Sixty-eight per cent of cases were males; 32 per cent were females. None of the patients was Negro in spite of numerous Negro patients in the other clinics. The average age in the chronic group was 52.9 years, and under nine years in the acute group. Practically all patients received P^{32} orally with doses of about 0.1 mc. per kg. of body weight, dividing the dose into individual daily doses as close to 1.0 mc. as feasible. Since 20 to 25 per cent of P^{32} is lost in feces, these small daily increments allowed for absorption of 75 to 80 per cent of the total dose.

P^{32} showed no beneficial effect in any of the acute cases. The authors emphasize the difference in survival rates depending on whether these are computed from the date of first hospital visit (11.3 per cent five year survival) or from the onset of the first symptoms (24.5 per cent). A list of the various complicating diseases associated with leukemia shows the frequent incidence of double primary neoplasms, and a significant number of intercurrent septicemias and bacterial infections. In only 2 patients of the chronic group was a terminal, acute picture of the

disease observed. Two patients experienced radiation illness after P^{32}. In 85 per cent, P^{32} caused at least a transitory fall in total peripheral white blood cell count. In 50 per cent, the hemoglobin and red blood cell count were not altered significantly in either direction. Adenopathy and splenohepatomegaly were affected inconstantly and often not at all measurably due to limited beta penetration power of P^{32}. The average survival time for 53 patients in the chronic group was 2.4 years following first hospital visit or 4.2 years following the onset of symptoms.—*J. A. Campbell, M.D.*

Kiehn, Clifford L., Friedell, Hymer, Benson, Jerrel, Berg, Marvin, and Glover, Donald M. A study of the viability of autogenous frozen bone grafts by means of radioactive phosphorus. *Ann. Surg.*, Sept., 1950, *132*, 427–431.

This is a study on the observations of the effects of autogenous bone grafts which, during storage, had been refrigerated in a deep freeze unit at 0° C. for periods of time ranging from two to six months. The grafts were obtained from the ilia of dogs; they contained both cortical and medullary bone. The grafts, following storage, were implanted separately in the subcutaneous tissues of the chest wall of the same animals from which they were originally taken. Immediately after implantation, the animal was given 200 microcuries of radioactive phosphorus intravenously.

After five to seven days, the grafts were found to be intimately associated with the tissues of the animal, and it was no longer easy to remove them without excising a portion of the surrounding tissue. This intimate association of the fragments with the tissues of the animal became more marked with time, and they ultimately became surrounded by a thin layer of cortical bone. Experiments were carried out with the bone grafts being boiled for forty-five minutes before implantation. The boiled grafts did not become intimately associated with the surrounding tissues. A thick fibrous capsule was formed around the graft, but it could be shelled out very easily from its bed five weeks after implantation.

The bone samples, after removal from the animal, were ashed at 700° C. The residue was then put into solution with nitric acid to facilitate uniformity among samples. After the specimens were properly prepared, they were counted by an ordinary Geiger-Müller counter. The rate of the uptake of radiophosphorus appears almost surely to be related to the metabolic activity of the bone, and begins as early as the second day. Boiled bone takes up some of the P^{32} (probably by simple organic exchange) and compares favorably with the observations that there is some fibrous tissue capsule and foreign body reaction around the devital bone. The uptake of radiophosphorus in the control grafts and the frozen bone continues to rise from the beginning, indicating clear-cut utilization of the available phosphorus. The rate of utilization of P^{32} in both the control and the frozen bone appears to be similar. The frozen bone implant, however, never reaches the level observed in the control bone. This apparently is due to the fact that the blood supply to the graft is not completely established, and does not permit the rapid exchange of metabolites which occurs in the control bone.—*E. A. Addington, M.D.*

Warren, Shields, MacMillan, Jane C., and Dixon, Frank J. Effects of internal irradiation of mice with P^{32}. Part I. Spleen, lymph nodes, thymus, bone and bone marrow. *Radiology*, Sept., 1950, *55*, 375–389.

In order to check sites and degree of radiation injury from P^{32}, carrier free P^{32} was injected subcutaneously into mice in doses of 2 millicuries which produced 100 per cent deaths in six days, 250 microcuries which produced 50 per cent deaths in eighteen days, and 25 microcuries. The effects on spleen, lymph nodes, thymus, bone and bone marrow are reported; other organs are to be reported at a later date. Radioactive phosphorus (P^{32}) emits only soft beta rays with maximum penetration of 8 mm. and has a half-life of 14.2 days, making it ideal for study of concentration and effects in specific organs.

In evaluating the results, the 250 microcurie dose gave the most information, the heavier dose showing faster and more complete destruction and the lighter dose showing lesser changes and more rapid and complete recovery. In general, the lymphocytes were destroyed first, then the other types of cells present in the organ, and lastly, the stroma cells. The spleen, thymus, and bone marrow showed maximum destruction two to ten days with return to essentially normal appearance in 50 plus days. However, the lymph nodes, after showing maximum destruction in five to ten days, did not return to normal function in ninety days, even after the minimum dose of 25 microcuries. One mouse treated with 25 microcuries developed a lymphoma.—*M. B. Goodwin, M.D.*

Warren, Shields, MacMillan, Jane C., and Dixon, Frank J. Effects of internal irradiation of mice with P^{32}. Part II. Gonads, kidneys, adrenal glands, digestive tract, spinal cord, lungs, and liver. *Radiology*, Oct., 1950, *55*, 557–570.

The study of the effect of radioactive phosphorus (P^{32}) on the histological structure of tissues of mice in dosages of 25, 250, and 2,000 microcuries is continued. Reduction in the amount of tissue is the most consistent effect on the ovaries. The number of graafian follicles is reduced, the corpora lutea disappear, the stroma is condensed with later development of interstitial tissue, but the absolute

sterilizing dose short of death has not been found in mice. In the testis, the spermatogonia are first affected, thereby interrupting the series to the sperm, the interstitial cells show increase in number, size, and vacuolization, and the Sertoli cells are relatively resistant. Only temporary sterility is produced and spermatogonia were regenerating fifty days following the sublethal dose of 250 microcuries. The kidneys showed only a transient effect on the tubules and the adrenals and lungs were practically unaffected. The digestive tract showed edema, desquamation, and slight hemorrhage following the lethal dose and only slight desquamation following the 250 microcurie dose. The liver showed compensatory ectopic hematopoiesis and minimal changes in the parenchyma.—*M. B. Goodwin, M.D.*

Storaasli, John P., Krieger, Harvey, Friedell, Hymer, L., and Holden, William D. The use of radioactive iodinated plasma protein in the study of blood volume. *Surg., Gynec. & Obst.*, Oct., 1950, *91*, 458–464.

In recent years the importance of the circulating blood volume and its relationship to disease has become more evident. The direct method for determining blood volume, which is of importance clinically, depends upon the dilution of a test substance injected into the blood stream. The requirements of an ideal test substance are that: (1) it remain in the vascular system for a relatively long period; (2) it mix readily with the normal constituents of blood; (3) it be easily identified and measured; and (4) it be non-toxic.

Summary. A method of determining the plasma volume of patients has been presented. It involves the measurement of the dilution of protein tagged with radioactive iodine after intravenous injection. Dilution is determined by measuring iodinated protein labeled with radioactive iodine before the injection and plasma periodically after the injection.

The technique of the procedure is simple and subject to small error. Repeated determinations can be performed within a short time.

The stability of the iodinated protein and its relatively secure retention within the vascular system permit a more accurate estimate of the plasma volume than has hitherto been possible. This method is probably of no more value than others when there is marked disturbance of normal physiology, as in profound shock, or in the other conditions which affect capillary permeability.—*Mary Frances Vastine, M.D.*

Dudley, H. C., Imirie, G. W., Jr., and Istock, J. T. Deposition of radiogallium (Ga^{72}) in proliferating tissues. *Radiology*, Oct., 1950, *55*, 571–578.

The selective deposition of radiogallium (Ga^{72}) is studied in mammals, chiefly mice. The high energy gamma rays of the isotope, which has a half-life of 14.3 hours, emits 2.5 mev. gamma rays and 3.1 mev. negative beta rays, makes possible a counting error of less than 10 per cent. Radioautographs have shown that gallium is deposited mainly in bone. By means of radioautography, sectioning and counting, it is shown that the epiphyseal junctions of long bones concentrate approximately four times as much gallium as does cortical bone. By means of an improved technique (impregnation of bone sections with liquid photographic emulsion) radioautographs magnified 100 times are obtained which show that radiogallium concentrates in areas of osteogenic activity. This is further borne out by the concentration of Ga^{72} in osteogenic sarcoma of mice and in the callus of healing fractures. The few non-osteogenetic tumors available showed no differential concentration and the mouse osteogenic sarcoma showed diminished concentration after repeated transfers, correlating well with its decrease in osteogenic activity.

Clinical tracer studies are being carried out but the toxicity of gallium prevents therapeutic trial. If the Ga^{72} can be concentrated by removal of the inactive Ga^{71} by electromagnetic means before administration, therapeutic dosages might be given without approaching the toxic concentration of gallium.—*M. B. Goodwin, M.D.*

Lawrence, John Hundale. The clinical use of radioactive isotopes. *Bull. New York Acad. Med.*, Oct., 1950, *26*, 639–669.

Radioactive isotopes have opened new applications of the "tracer" technique for the biologist and physiologist and have provided new sources for radiation therapy.

Damaging effects and induction of neoplastic changes by radioactive sources are discussed and the "safe tracer dose" defined as the amount that will deliver to the body less than 0.1 roentgen of total body irradiation in a twenty-four hour period.

P^{32} labeled red cells, reinjected, enable a determination of the blood volume by the simple dilution technique. Then, with the aid of the hematocrit, one can determine the total red cell mass, total plasma volume and total blood volume. Former methods do not give an accurate picture, either of the red cell mass or the plasma volume. These values are of importance in polycythemia and chronic leukemia. The same reinjection technique, prior to sternal marrow aspiration, enables determination of the percentage of peripheral blood in the marrow specimen.

Radioactive water, CO, NaCl and P^{32} labeled red cells have given information as to the rates of mixing of these substances in normal and abnormal subjects. In cardiac patients in failure, all components of the mixing and excretion curves are slowed. In

those without edema, the extracellular fluid is normal. In those with edema, the extracellular fluid is 23 per cent (normal, 17 per cent). Nephritics with edema, with normal cardiac function, have increased extracellular fluid, but normal mixing times.

Using Fe^{59}, clearance of iron from the blood plasma was studied. The life of the normal red cell was determined to be 120 days. Patients with polycythemia, leukemia and pernicious anemia cleared iron from the plasma more rapidly than normal, indicating a short red cell life. The aplastic anemia group showed slower clearance.

Using radioactive carbon in the carboxyl-carbon position, exhaled CO_2 gave evidence of the presence, in a mouse, of an extremely small transplanted mammary tumor. P^{32} indicated an abnormal metabolism of desoxypentose nucleic acid in a mouse with an extremely small mammary tumor.

Studies have been made of the circulation of the extremities and of the heart in various conditions and of the metabolism of lipoproteins in atherosclerosis.

By inducing radioactivity in a biological sample, then extracting for various substances, their presence can be detected with a sensitivity that may be many times that of any other standard procedure for microchemical analysis.

For therapy, one would desire a radioactive compound which would localize in the neoplastic cell only and which would emit a ray which would dissipate all of its energy in one cell diameter. P^{32} localized in rapidly growing tissues and in the bone and bone marrow cavities. Of animals with leukemia, 15 per cent survived treatment with P^{32} and were rid of the disease. Humans with leukemia treated with P^{32} showed somewhat better end results than with any other treatment.

P^{32} has been most successful in polycythemia vera. Approximately 150 patients have been treated in eleven years. On the average, treatment was necessary every three years. There has been no evidence of irradiation-induced neoplasms and the incidence of late leukemia is lower than in patients treated otherwise. Hodgkin's disease, lymphosarcoma and multiple myeloma are no longer being treated by P^{32} because results are not significantly better than with roentgen treatment.

P^{32}, pipetted onto blotting paper, has been used to treat superficial skin cancer. The dose is 5,000 to 10,000 r in seventy-two hours. Radioactive iodine is used in the treatment of cancer of the thyroid and its metastases.

From the experience of the past fifteen years, there is little question that if one can get localization of radioactive materials in cancer tissue—50 or more times the concentration in normal tissues—definite therapeutic benefits in hopeless cancer patients can be obtained, particularly if radioisotopes with soft beta rays, such as H^3 and C^{14} are used.—*T. J. Wachowski, M.D.*

Gorbman, Aubrey. Functional and structural changes consequent to high dosages of radioactive iodine. *J. Clin. Endocrinol.*, Oct., 1950, *10*, 1177–1191.

The author developed a "thyroid-toxic dose" of I^{131} for mice caused by 4 microcuries per milligram of thyroid tissue. This dose destroyed all thyroid follicles in two to three weeks. He found that varying amounts of iodine in the diet caused a variation in the maximum thyroid uptake, the range being 1 to 58 per cent.

I^{131} injured thyroid tissue showed no evidence of regeneration nor of metaplasia after eighteen months. There was only 1 per cent of the I^{131} uptake of normal glands. In the mouse, adjacent soft tissues were injured, probably because of the minute spatial relations. Reproduction was virtually halted due to almost complete absence of ova. The males were unaffected. Acute glomerulonephritis and periportal cirrhosis were noted with residual fibrous liver scars. Treated mice attained 80 per cent of normal growth.

Eight months after "thyroid-lethal doses," more than 90 per cent of treated mice developed a noninvasive chromophobic tumor of the anterior pituitary gland. It grew to half the size of the brain, killing by pressure. Some physiological etiological mechanism seemed implied by its high incidence.—*T. J. Wachowski, M.D.*

Cantril, Simeon T. On the possible application of isotopes to the management of cancer. *Ann. Int. Med.*, Dec., 1950, *33*, 1450–1458.

Isotopes can be used in the field of investigation and in the therapeutic aspect of the cancer problem. The author calls attention to the recent great public interest in the cancer problem and in particular to the relationship between atomic energy and the solution of the cancer problem. He reviews in great detail the experiences which led earlier workers to abandon the introduction of radioactive substances into the system as a means of affecting the growth of tumors. He notes that a concept of biologic radiosensitivity formulated after the discovery of radioactivity has not been appreciably altered since the advent of atomic energy. He presents a large list of obstacles which must be overcome before the products of atomic energy can be useful in the treatment of malignant disease.—*R. E. Kinzer, M.D.*

Davis, Loyal; Martin, John; Ashkenazy, Moses; LeRoy, George V.; and Fields, Theodore. Radioactive diiodofluorescein in diagnosis and localization of central nervous system tumors. *J.A.M.A.*, Dec. 23, 1950, *144*, 1424–1432.

The authors discuss the history of the use of various dyes in the recognition and treatment of neoplasms. The physiology of fluroescein in recounted.

The localization of the dye in tumor tissue is related to the permeability of the capillaries. This abnormally high permeability leading to the escape of the dye is probably due to the "spreading factor" of the cancer.

Moore and his associates in 1947 were the first to use radioactive diiodofluorescein in the localization of brain tumor. The radioactive portion is I^{131}.

The technique and apparatus are described in detail. Briefly it consists of injecting 1.2 mc. of radioactive diiodofluorescein intravenously and measuring the uptake, after a suitable period, over 32 specific areas of the skull with a Geiger-Müller tube.

A difference of 50 counts per minute between symmetrical areas of the skull is arbitrarily considered to be the lower level of significance. All 32 areas must be counted in each case before the findings can be interpreted as significant.

The amount of radiation received by the tissue of the body is very minimal. The biologic half-life is two to three days. The highest concentration, after the initial maximum, occurs in the thyroid gland. The dose of radiation delivered in this tissue is from 1.9 to 3.8 roentgen equivalents.

Of 95 histopathologically verified space-occupying lesions of the central nervous system 86, or 91 per cent, were accurately diagnosed as organic and localized with radioactive fluorescein, while 4 diagnoses were completely inaccurate. The other 5 were inaccurate only insofar as the nature of the lesion was concerned but were accurate in respect to localization of the lesion.

Seventy-two cases were thought not to have a space-occupying lesion by this test, and this was corroborated by surgical exposure in 13, air studies in 54 and/or angiography in 5 instances.

In all 200 cases there were only 9 proved inaccuracies making a total accuracy of 95.5 per cent for the radioactive diiodofluorescein test. All but 1 of these 9 mistakes were also inaccurately diagnosed by clinical examination, electroencephalography, and pneumography. Most of the inaccuracies occurred in tumors and collections of blood which were cystic in character.

It was noted that the histopathology of central nervous system tumors could be suspected from the gradation of differential counts per minute over symmetrical areas of the skull. This was related not only to the degree of malignancy of the tumor but even more so to its angioarchitectural pattern and its degree of anaplasia. Metastatic carcinomas and sarcomas gave counts in the highest differential range. Next came glioblastoma multiforme and vascular and cellular meningiomas. The patients with astrocytoma and oligodendroglioma showed the lowest differential count of all the tumors. Recurrent gliomas had a much greater uptake of dye, which is consistent with their increased vascularity and cellularity. Chronic subdural hematomas and the extensively cystic tumors gave the lowest differential counts.

Radioactive dye studies are a great asset to the neurosurgeon because in most instances they precisely localize the tumor as to the lobe involved. There were 8 patients who had negative air studies in the presence of a verified tumor and in all but 1 of these the dye studies accurately diagnosed the lesion. Postoperative studies with radioactive dye are also valuable to determine the extent of the removal and also to detect recurrences.

Spinal cord tumors are difficult to localize and diagnose because gamma radiations are also being recorded from the adjacent liver, spleen, lungs and intestines. It would seem that under the present system only tumors removed from the chest and abdomen, such as cervical and lower lumbar tumors, can be accurately localized and detected.—*R. A. Hays, M.D.*

Chester, J., Lerch, P., and Vannotti, A. A propos du traitement par l'ioderadioactif du cancer et des métastases d'origine thyroïdienne. (Concerning the treatment of cancer of the thyroid and its metastases with radioactive iodine.) *Schweiz. med. Wchnschr.*, Dec. 30, 1950, *80*, 1377–1381.

A woman with adenocarcinoma of the thyroid (papillary type) was treated with radioactive iodine as she developed multiple osseous and pulmonary metastases about two years after a subtotal thyroidectomy. Five doses of I^{131} (from Harwell, England) varying from 1 to 3 mc. were used within a period of seven weeks. The following observations were noted: (1) the normal portion of the thyroid fixed most of the radioactive iodine; (2) within two weeks, at the third dose and after, there was considerable reduction in the fixation of I^{131} by the thyroid because of the destruction of the gland by the previous doses; (3) the metastatic foci did fix the isotope to an important degree but lost it very rapidly beginning with the sixth hour so that after forty-eight to seventy-two hours only 15 to 30 per cent of the initial radioactivity could be measured.

On the basis of these observations, correlated with the findings of American authors, the authors came to the following conclusions: (a) for an optimum dose the volume of the metastases should be taken into consideration; (b) the thyroid deprives the metastatic foci from the greater part of the ingested radioactive iodine (hence the necessity of total thyroidectomy which is preferable to the radiological destruction of the gland); (c) the elimination of the isotope in the urine should be calculated if the quantity fixed is going to be computed; (d) the amount of the fixed isotope in the metastatic foci and the duration of the fixation in these lesions should be determined so as to ascertain the effectiveness

of the treatment. If the fixation in the metastatic foci lasts for only a few hours, as was observed by the authors, it is useless to use I^{131}.—*J. N. Sarian, M.D.*

Freedberg, A. Stone, Blumgart, Herrman L., Kurland, George S., and Chamovitz, David L. The treatment of euthyroid cardiac patients with intractable angina pectoris and congestive failure with radioactive iodine. *J. Clin. Endocrinol.*, Oct., 1950, *10*, 1270–1281.

It has been noted that (1) the velocity of blood flow was considerably slowed in patients with congestive heart failure and normal basal metabolic rates, the retardation in the velocity of blood flow generally paralleling the degree of circulatory insufficiency; (2) the velocity of blood flow in myxedema, in the absence of circulatory insufficiency or congestive heart failure, showed a degree of slowing similar to that in patients with congestive heart failure. It was thought that (1) if the normal metabolic rate of the patient with congestive heart failure (or angina pectoris) were reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of his body, and (2) the metabolic demands would be reduced to a level to conform to the blood supply.

Relief has been given more than 50 per cent of 350 patients with intractable angina pectoris or congestive heart failure, subjected to total thyroidectomy. The magnitude of the procedure in such seriously ill patients militated against the practicability of its use. Thiourea compounds succeeded in inducing hypothyroidism in some patients only. Dangerous drug reactions occurred or could occur during the prolonged (continuous) therapy.

Since August, 1947, hypothyroidism has been induced in 23 euthryoid patients for from three to twenty-three months, average 15.5 months. Each patient received orally a total of from 25.5 to 176.0 mc. of I^{131} in single or divided doses. The largest single dose was 56 mc. The average total dose was 61 mc. In 8 patients, the calculated dose to the thyroid gland was from 28,800 to 56,100 rep. In three patients, hypothyroidism was induced in from nine to fourten weeks with 28,300 to 43,700 rep.

Angina pectoris has been strikingly lessened or abolished in 11 of the 17 patients with intractable cardiac pain. Concomitant congestive heart failure, present in several of these patients, was likewise improved. In the other 6 patients, angina pectoris was relieved when the patients were myxedematous, but recurred when desiccated thyroid was administered in order to ameliorate the discomfort of myxedema.

Four of 6 patients, incapacitated primarily because of congestive heart failure, have shown worth while improvement; in 3 of these the improvement has been striking.—*T. J. Wachowski, M.D.*

Tivey, Harold, and Osgood, Edwin E. The biological half-life of radioactive phosphorus in the blood of patients with leukemia. I. Whole blood—with deviations of observations from predicted values and an estimate of total-phosphorus turnover rate. *Cancer*, Nov., 1950, *3*, 992–1002.

The P^{32} level of whole blood is a function of the added P^{32} concentration of plasma, erythrocytes, and leukocytes.

This study represents the results in chronic granulocytic or lymphocytic leukemia treated with P^{32} in small, regularly spaced doses. The P^{32} was administered intravenously in a concentration of 1 mc. per cc. of sterile isotonic solution. The method of preparing and counting the blood samples is described.

Results indicate that the logarithm of the P^{32} concentration decreases uniformly with time and that the time required for the blood level of P^{32} to reach half its original value is approximately eight days—the biological half-life.

One-half the phosphorus atoms in the blood are replaced in nineteen days, while the apparent average life of the phosphorus atom in the whole blood of this series of leukemia patients is twenty-seven days.

The observations that higher initial levels of P^{32} have attending shorter half-lives and that the individual differences in P^{32} metabolism account for the variations in the half-life curves of the patients are discussed. In turn, 53 per cent of the injected P^{32} in microcuries per gram of body weight represents the calculated initial concentration in microcuries per milliliter of whole blood. Two equations and a chart are presented which permit the calculation of P^{32} levels in the blood at time intervals and the determination of the blood levels at any given time, having known one blood concentration. Individual variations, however, limit this process.

Many statistics are presented in graphic form with an analysis of each in the written text.—*J. W. Wilson, M.D.*

Osgood, Edwin E., and Tivey, Harold. The biological half-life of radioactive phosphorus in the blood of patients with leukemia. II. Plasma—with deviations of observations from predicted values and an estimate of total-phosphorus turnover rate. *Cancer*, Nov., 1950, *3*, 1003–1009.

As in Part I, the experimental and statistical methods employed are described at some length. In a manner similar to that observed in whole blood, the logarithm of the plasma P^{32} level decreases uniformly with time, the biological half-life being 8.5 days. Unlike the whole blood studies, however, the zero-time level in microcuries per milliliter represents 16 per cent of the injected P^{32} in microcuries per gram of body weight; therefore, the phos-

phorus per cc. of plasma is approximately 31 per cent of the total phosphorus per cc. of blood.

One-half the phosphorus atoms were found to be replaced in approximately twenty-one days by the non-radioactive phosphorus compounds entering and leaving the plasma. This was suggested by the parallel curves of the disappearance of P^{32} in whole blood and plasma, indicating an equilibrium between the phosphorus-containing compounds of the plasma and whole blood.

As in Part I, the plasma P^{32} levels showed considerable individual variations. However, the curves for any given individual could be predicted with an error of less than ± 15 per cent. A recognition of these variables is necessary in proposing P^{32} therapy.—*J. W. Wilson, M.D.*

Tivey, Harold, and Osgood, Edwin E. The biological half-life of radioactive phosphorus in the blood of patients with leukemia. III. Erythrocytes—with deviations of observations from predicted values. *Cancer*, Nov., 1950, *3*, 1010–1013.

The purpose of this study was to determine the rate of disappearance of P^{32} from the erythrocytes of leukemic patients as correlated with the plasma levels of P^{32} in these same patients. Specimens were taken in the intervals between treatments for periods of from one to six weeks.

Equilibrium was found to exist between total plasma P^{32} and erythrocyte P^{32} seventy-two hours following administration. Likewise, there was no significant variation in the decrease of P^{32} in erythrocytes and plasma of patients with lymphocytic as compared with patients with granulocytic leukemia.

The logarithms of 151 observations of P^{32} levels were plotted against time and the curve was seen to be a linear function of time. The biological half-life of 50 per cent of the initial level of P^{32} in erythrocytes according to this curve is 8.9 days.

Disappearance of P^{32} from both plasma and erythrocytes seventy-two hours following injection occurred at such a uniform rate that the median ratio of erythrocyte P^{32} per cc. over plasma P^{32} per cc. was 6.1:1. This compares with the ratio taken from the literature of total phosphorus per cc. of "cells" to total phosphorus per cc. of plasma which is 6.2:1.

A curve is presented to show the distribution of deviations from values which were predicted.—*D. E. Vivian, M.D.*

Osgood, Edwin E., and Tivey, Harold. The biological half-life of radioactive phosphorus in the blood of patients with leukemia. IV. Leukocytes—radioactive phosphorus content and the relation to plasma-P^{32} levels. *Cancer*, Nov., 1950, *3*, 1014–1017.

In this study the authors determined the rate of disappearance of P^{32} from unit volumes of leukocytes of leukemic patients as correlated with the plasma levels of P^{32} in these same patients in the intervals between doses of P^{32} administered for the treatment of leukemia.

Due to the technical difficulties in carrying out this investigation large errors were present. Consequently the authors consider this only an inadequate approach to the problem and present these data only as an interim report with a more detailed report to follow.

From 116 determinations of P^{32} levels in both lymphocytic and granulocytic leukemia patients it was found that for clinical purposes the leuckocytes contain approximately thirty times the P^{32} found in a similar volume of plasma after seven days following administration of P^{32}. However, individual ratios vary from 10:1 to 50:1. Likewise it was found that while the partition of P^{32} in granulocytes was proportional to the total phosphorus, the same was not true in lymphocytes; much less was found than anticipated in the latter case.

The authors indicate more precise information on this subject can be expected following investigations now in progress on phosphorus metabolism in leukocyte nucleic acids of leukemic patients.—*D. E. Vivian, M.D.*

Hahn, P. F., Wells, E. B., and Meneely, G. R. The circulating red cell mass in polycythemia vera as determined by red blood cells tagged with the radioactive isotope of iron. *South. M. J.*, Nov., 1950, *43*, 947–950.

The authors present 2 cases of polycythemica vera and describe a more accurate method of determining the total red cell mass. There is also a short discussion of the disease in general and of some therapeutic problems. Most physicians treat polycythemia by phlebotomy and are guided by the venous hematocrit. Such a procedure would be valid only if the relationship between the hematocrit and cell mass were known to be similar to that existing under normal conditions.

The authors show that the average body hematocrit of the circulation is approximately 20 per cent below that found in the venous large circulation; also the hematocrit is much lower in the capillaries, venules and arterioles than for the average body hematocrit in order to account for the average of the large and small vessels.

Polycythemia is characterized clinically by three main features: (1) marked increase in the peripheral circulatory red blood cell count and venous hematocrit, (2) plethora, and (3) clinical absence of a demonstrable cause of secondary polycythemia. In one case treated by phlebotomy in the usual manner, a total of 4,000 ml. of blood was removed over a period of eleven days. Eight days later, the venous hematocrit had reduced from 67 per cent to 46 per

cent. However, at this reading, the patient exhibited the same amount of plethora as before. The authors feel that in such a case the patient was undertreated by the use of phlebotomy. The red cell tagged with radioactive iron gives a much more accurate determination of red cell mass. The cell mass is much greater than would be expected and as a result more complete and accurate treatment can be carried out.

The method of determining the cell mass by radioactive studies is described.—*J. G. Snead, M.D.*

Williams, G. Z., Stanton, A. C., Jamison, R. M., and Williams, J. T. The distribution of radioactive gold colloid in rats, mice, and transplanted mouse tumors. *South. M. J.*, Dec., 1950, *43*, 1031–1038.

This report includes the preliminary results of investigation to determine the effects of irradiation of cancer by colloidal gold. Radioactive gold (Au^{198}) emits relatively low energy beta rays (0.8 mev.) with a short range of 8 mm. in water and tissue. The gamma rays, likewise, are of low energy (0.44 mev.) and the half-life is short enough (2.7 days) to be convenient for experimental and therapeutic use.

Tracer doses of from 20 to 100 microcuries and therapeutic doses of 1 millicurie per animal (average weight 25 grams) were tested for distribution and biological radiation effects by intraperitoneal, intracardiac, and intrasplenic injections and by subcutaneous and tumor infiltration. A total of 287 mice and 40 rats were injected. At varying intervals after the injection small blood samples were taken, dried to constant weight rapidly, weighed, and counted.

In both rats and mice biological decay of gold sol is relatively slight. In no instance was there loss of radioactive gold through the urine and stools greater than 2.2 per cent of the injected dose during the first week, after which the counts were in the order of background. With doses of 1 millicurie into the spleen or heart of the rats there was slight radioactivity of the stools from one to eight days following which they became inactive. Peak excretion occurred consistently at five days. The total activity of the stool was about 1.8 per cent of the injected dose and the urinary output was 0.4 per cent or less.

The authors found that following injection by intracardiac and intraperitoneal routes the Au^{198} was taken up chiefly by the liver and spleen with the highest concentrations almost always in the liver, being retained by the Kupffer and reticuloendothelial cells. However, in the instances of intrasplenic injections frequently larger proportions remained in the spleen for several days. The colloidal particles were taken up by the phagocytic cells and it was noted that more than 97 per cent of the radioactive gold colloid injected by various routes was retained within the tissues indefinitely. It is conceivable that with high doses there might be injury and destruction of the phagocytic cells to such extent that there may be higher levels of excretion due to failure of the retaining mechanism.

When various tumors, carefully injected with small doses of radioactive gold colloid, were transplanted into mice, it was noted that necrosis and vascularity of the tumors greatly influenced the leakage of the radioactive gold colloid into the general circulation and that ultimate loss occurred, particularly when large necrotic tumors were injected. The locally injected, solid cellular tumors retained the sol well (80–100 per cent), only small amounts escaping into the general circulation. Uniform distribution in the tumors could not be obtained and complete regression of all tumors was not possible. The distribution was determined by radioautographs.

Local injections of 200 to 500 microcuries of the active colloid into sarcoma 180 and sarcoma 37 resulted in satisfactory regression. The best results were obtained with a dose of 400 microcuries (30,000 rep of beta radiation per gram); a dose of 200 microcuries also gave satisfactory results where carefully infiltrated. The average weight of the tumor was 1 gram.

The authors also used nitrogen mustard in combination with radioactive gold sol infiltration and found that the results were better when both were used together than when each was used alone.

There are numerous charts and graphs.—*J. G. Snead, M.D.*

CHEMOTHERAPY

Reveno, William S., and Rosenbaum, Herbert. Treatment of hyperthyroidism with 1-methyl-2-mercaptoimidazole. *J.A.M.A.*, Aug. 19, 1950, *143*, 1407–1408.

The authors used 1-methyl-2-mercaptoimidazole (tapazol) in the treatment of 18 patients with hyperthyroidism during a six month period and found it as effective as thiouracil or propylthiouracil in this condition. Toxic reactions were not observed but the authors believe that further time and more cases are needed to evaluate this more completely. Tapazol is twenty-five times more potent than thiouracil. Four cases were presented and discussed. —*C. W. Cooley, M.D.*

Klopp, Calvin T., Alford, Crandall, Bateman, Jeanne, Berry, G. Neill, and Winship, T. Fractionated intra-arterial cancer chemotherapy with methyl bis amine hydrochloride; a preliminary report. *Ann. Surg.*, Oct., 1950, *132*, 811–832.

The intra-arterial injection of HN_2 in regional cancer therapy is discussed. Both experimental and clinical studies were carried out. An artery furnishing the blood supply to the neoplasm was selected.

A polyethylene tube was introduced into the artery and held in place with ligatures. HN_2 was then injected into the polyethylene tube at intervals of from eight to twelve hours for a period of time varying from six to twenty-two days. Ten cases of neoplasm were given this therapy. All had relief from pain. There was evidence of selective action on neoplastic tissue within the area supplied by the injected artery. Gross and microscopic regression of the lesions has been demonstrated.

The authors conclude that their experience is limited and until many problems, mentioned in their report, have been solved, regional intra-arterial cancer chemotherapy must be considered as an experimental procedure.—*C. P. Truog, M.D.*

King, Walter G. Treatment of far advanced carcinoma of the breast: present status of testosterone therapy. *Arch. Surg.*, Oct., 1950, *61*, 630–653.

Testosterone is stated to be of maximum value in patients with far advanced carcinoma of the breast with a variety of metastases when (a) all the surgical treatment practicable has been completed; (b) benefits possible from roentgen therapy have been exhausted; (c) establishment of a post-menopausal status, either natural or from irradiation or surgical castration, has been brought about before the start of testosterone, and (d) there has been development of pain of cancer origin requiring narcotics for relief and/or disability requiring nursing care.

The present study was carried out when possible as a "demand therapy" plan of administration of androgen. An average dose of 250 mg. of testosterone propionate in oil was given per week. In the group of patients studied here, further beneficial effect was not derived from the increase of the average dose to over 300 mg. per week.

By treatment with testosterone as outlined, 7 of 13 patients with far advanced, painful and/or disabling cancer of the breast, who lived over thirty days after the start of therapy, were temporarily improved for an average period of over a year. An additional 4 patients received enough benefit to have justified the use of the androgen.—*J. J. McCort, M.D.*

González Martínez, I., Malaret, Pedro S., Taveras, J., and Hazim y Lourdes, P. Olivencia. Contribución al conocimiento de las indicaciones y efecto del nitrógeno de mostaza (Methyl-bis Merck) en el tratamiento de ciertas enfermedades del sistema reticulo-endotelial. (Contribution to the knowledge of indications and effect of nitrogen mustard [Methyl-bis Merck] in the treatment of certain diseases of the reticulo-endothelial system.) *Rev. Liga puertorriq. contra el cáncer*, April, 1950, *10*, 31–69.

Three cases of Hodgkin's disease, 3 cases of lymphosarcoma and 4 cases of leukemia were treated with nitrogen mustard intravenously. The dosage depended on the weight of the patient but never exceeded 5 milligrams. Each patient received a total of five injections, distributed over a period of five consecutive days.

Severe reactions (nausea, vomiting, fever, headache, general weakness and restlessness) were, as a rule, observed three or four hours after injection. One case showed no untoward symptoms.

In the cases of Hodgkin's disease, nitrogen mustard influenced the fever favorably, at least in the beginning. It also seemed to stimulate the appetite but, while being a coadjuvant of roentgen therapy, it cannot be considered to have any effect on the final outcome of the disease.

No results were noted in lymphosarcoma.

In 2 cases of chronic myelogenous leukemia, 1 patient showed some improvement but less marked than observed after roentgen therapy. In the second case of chronic myelogenous leukemia and in a case of acute myelogenous leukemia the nitrogen mustard treatment resulted in failure. Favorable results were noted in chronic lymphatic leukemia. The authors therefore conclude that nitrogen mustard appears indicated in the chronic leukemias but is definitely contraindicated in the acute forms of leukemia.—*E. A. Schmidt, M.D.*

McNeil, D. L. Acute leukaemia with a folic acid antagonist. *Canad. M. A. J.*, Sept., 1950, *63*, 284–287.

Folic acid antagonists have produced remissions in a reasonably good proportion of cases with acute and subacute leukemia. The drugs offer no cure and relapses occur when treatment is stopped, and in other cases even though treatment is continued.

The author reports a series of 7 cases treated with aminopterin. One of these had a good response with a remission of eight months. The drug did not produce any apparent change in the course of the disease in the other 6 patients.

The toxic effects resemble those of folic acid deficiency states. The more common findings are bone marrow aplasia, stomatitis, pharyngitis, diarrhea and gastrointestinal hemorrhage. Most cases shows a marked reduction in the white blood cell count but without any apparent increase in the normal cells.—*A. E. Imler, M.D.*

Skipper, Howard E., Chapman, Juanita B., and Bell, Martelia. Studies on the role of folic acid in the leukemic process. *Cancer*, Sept., 1950, *3*, 871–873.

This is a very brief report on the effect of folic acid in accelerating the leukemic process and decreasing the survival time of AK 4 strain leukemia in mice. As was expected, the use of the folic acid

antagonist, aminopterin, increased the life span significantly and the results appeared to be statistically of definite value.

Apparently this is a preliminary report, the object being to obtain a better understanding of the biochemical mechanism of the action of aminopterin. The authors are now employing tracer studies in the approach to this problem.—*M. M. Manalan, M.D.*

Pearson, O. H., and Eliel, L. P. Use of pituitary adrenocorticotropic hormone (ACTH) and cortisone in lymphomas and leukemias. *J.A.M.A.*, Dec. 16, 1950, *144*, 1349–1353.

The authors studied the response to pituitary adrenocorticotropic hormone and cortisone acetate in 70 patients with various types of neoplastic diseases at Memorial Hospital during the course of two years. The mechanism by which adrenal hormones exert their physiological effects is not known. Albright believes that tissue atrophy results from inhibition of tissue synthesis rather than stimulation of tissue breakdown. Animal studies have demonstrated that either hormone produces atrophy of lymphoid tissue. The following clinical observations were made by the authors:

Chronic lymphatic leukemia. Considerable shrinkage in the size of the enlarged lymph nodes, spleen and liver was observed from 100 to 200 mg. of ACTH or cortisone acetate given daily for eighteen days to three months. Recurrence occurred in some cases in from six weeks to three months.

Patients have responded equally well to three courses of hormone therapy, indicating that refractoriness does not develop. Initially the peripheral white blood cell count rose, at times to two or three times its original level, and then gradually fell to below the pretreatment level. There was no improvement in the differential blood count. Subjective improvement was noted in all patients. The results indicated that complete remissions are not obtainable with these hormones but palliation is effected.

Lymphosarcoma. All patients showed definite shrinkage of lymphoid tumor masses. Usually there was a regrowth of the tissue in about four months after the cessation of therapy. Biopsy of the lymph nodes after shrinkage revealed no essential pathologic alteration. The results were not encouraging but the method will probably be an excellent adjunct to radiation therapy.

Acute leukemias. Temporary remissions were induced in both children and adults afflicted with acute granulocytic or acute lymphocytic leukemia. Monocytic leukemia appeared to be unaffected by these hormones. Symptomatic improvement usually occurred within the first few days of treatment. There was cessation of bleeding and shrinkage of the enlarged lymph nodes, etc. Hematological improvement was first manifested by a rapid fall in the number of circulating white blood cells and an increase in the percentage of mature cells. Blood picture was frequently normal in two to four weeks, even the bone marrow may approach normal.

Remissions thus induced were of short duration, varying from three weeks to two months. In these diseases, refractoriness to hormonal therapy developed rapidly.

Hodgkin's disease. The results in this disease were not spectacular. There was some shrinkage of the enlarged lymph nodes which was temporary and not very marked.

Plasma cell myeloma. In 1 case treated there was a rapid disappearance of the severe pain in the extremities and back, a decided reduction of serum myeloma protein and improvement in the blood picture. Exacerbations occurred promptly after withdrawal of the drug.

In the following neoplastic diseases there was no improvement: chronic myelogenous leukemia, carcinoma of the breast, lung, prostate, pancreas and adrenal, Ewing's sarcoma, osteogenic sarcoma, synovial sarcoma, neuroblastoma and malignant melanoma.

The authors discuss the undesirable side effects of both hormones. These simulate the signs and symptoms of Cushing's syndrome rather closely.—*R. A. Hays, M.D.*

MISCELLANEOUS

Moore, G. E., Kohl, D. A., Marvin, J. F. Wang, J. C., and Caudill, C. M. Biophysical studies of methods utilizing fluorescein and its derivatives to diagnose brain tumors. *Radiology*, Sept., 1950, *55*, 344–362.

Fluorescein does not penetrate the so-called blood-brain barrier probably because of the negative charge on its chromagen portion. Any process, such as brain edema, brain abscess, subdural hematoma, granuloma, trauma, and neoplasm, which breaks down this barrier will allow the anion to pass into the tissues of the process. Hence, if sodium fluorescein is injected into the blood stream, the fluorescein anion will be concentrated differentially in the area of pathology as compared to normal brain tissue. The above fact has been used in localization of brain tumors and the paper deals with the detection of the dye. Since fluorescein fluoresces in ultraviolet light, this method has been used at the time of surgery to help localize the tumor, the accuracy being approximately 95 per cent in 104 cases, the slower growing and necrotic tumors sometimes not absorbing the dye differentially.

An attempt at roentgenographic visualization of tumors by labeling the fluorescein with atoms of higher atomic number failed. Compounds containing heavy metals were too unstable under physiological conditions and hence quite toxic. Tetraiodofluores-

cein would require an almost impossible concentration for deteetion by present means. Skiodan and iodinated salicylic acid also gave insufficient contrast.

Labeling with radioactive iodine (I^{131}) and detection with a Geiger-Müller counter proved more successful. Work is in progress on a practical scintillation type counter which has a better efficiency but also a troublesome background noise. Difficulties in keeping the cone of tissue exciting the counter as small as possible and still retaining a sufficient number of counts, and methods of surveying the skull are discussed. Simultaneous bilateral counting using the differential is recommended to minimize the decay factor. The accuracy of localization of a tumor following injection of radioactive fluorescein is dependent upon the size, location, type, and surrounding edema of the tumor. More accuracy may be expected upon the development of a practical scintillation type counter.

Normally about 15 per cent of the dye will be excreted by the kidneys and 75 per cent found in the feces. In patients with portal obstruction, 100 per cent is excreted by the kidneys.—*M. B. Goodwin, M.D.*

Fano, U., and Taylor, Lauriston S. Dosage units for high-energy radiation. *Radiology*, Nov., 1950, *55*, 743–747.

Because the mean penetration of the associated electrons from gamma radiation increases rapidly with the energy of the gamma rays, the flow of high energy roentgen or gamma rays at any one point is no longer related clearly and directly to the ionization produced or the energy dissipated at that point. The amount of energy dissipated at a given point by an ionizing radiation surely represents the most physically sound term of reference for discussing the effects produced by the radiation. However, at present, while cavity ionization determinations can be made fairly accurately, it is difficult to convert the amount of ionization into units of energy dissipation. Hence, the following recommendations to the International Congress of Radiology are made. (1) The roentgen be retained as a unit for roentgen-ray and gamma-ray quantity within the limits of radiation quality where it is practicable to meet the present definition, i.e., under 400 peak kilovolts. (2) For correlation with high energy radiations, the energy dissipated by the ionizing radiation expressed in ergs per second should be used. (3) Where (2) is impracticable, the dosage should be expressed in terms of quantity of charge of either sign separated per unit mass of gas in the ionization chamber. (4) The International Committee promote compilation and distribution of the best available data for conversion of (3) to (2).

These recommendations were adopted by the Sixth International Congress of Radiology, London, 1950.—*M. B. Goodwin, M.D.*

Sorrentino, Joseph, and Yalow, Rosalyn. A nomogram for dose determination in diagnostic roentgenology. *Radiology*, Nov., 1950, *55*, 748–753.

Using the inverse square law and an experimentally derived graph showing the relationship between dosage rate in milliroentgens per milliampere-second and the kilovoltage, the authors have constructed a monogram from which approximate (plus or minus 25 per cent) patient skin doses may be readily determined for any roentgenographic or fluoroscopic procedure. It was determined that the inverse square law held within plus or minus 10 per cent for tube patient distances from 15 to 36 inches and the remainder of the scale was filled in by extrapolation. The dosage rate with respect to kilovoltage at 30 inch distance correlated well with the data contained in the National Bureau of Standards Handbook 41. A table showing the various roentgenographic techniques used at the authors' clinic and the number of roentgens in air to which the patient is exposed for each examination is included. Since the accuracy is not better than plus or minus 25 per cent, a factor of 1.25 is suggested for determination of the actual skin dosage.—*M. B. Goodwin, M.D.*

Kane, Irving J. Tilt table attachment for chest planigraphy in upright and recumbent positions. *Radiology*, Dec., 1950, *55*, 886–889.

A tilt table attachment is described for body section roentgenography of the chest in the erect or the horizontal position. Three figures illustrating the various parts of the attachment are included, and should be studied by anyone interested in utilizing it.—*E. E. Seedorf, M.D.*

Carpender, J. W. J., and Lanier, Raymond R. The combined effect of a tumor inhibitor (5-amino 7-hydroxy-1 H-V-triazolo [d] pyrimidine) and x-ray therapy. *Radiology*, Dec., 1950, *55*, 874–878.

The success of irradiation in cancer therapy is dependent, in most instances, on the differential sensitivity of cancer cells as compared to the cells of normal surrounding tissue.

Groups of C 57 black mice bearing transplanted E 0771 adenocarcinoma were treated with guanazolo (an inhibitor of guanine metabolism) only, with roentgen rays only, and with guanazolo plus roentgen rays. Treatment with guanazolo alone, seven days after tumor inoculation, failed to arrest growth of the tumor, but tumors treated with guanazolo and roentgen rays were smaller than those treated by either guanazolo alone or roentgen rays alone.

This preliminary study indicates a synergistic effect between roentgen rays and guanazolo but the mechanism of this effect is unknown at present.—*E. M. Cooper, M.D.*

Dowdy, Andrew H., Bennett, L. R., and Chastain, Sarah M. Protective action of anoxic anoxia against total body roentgen irradiation of mammals. *Radiology*, Dec., 1950, *55*, 879–885.

The authors carried out a number of experiments in order to determine the effect of extreme anoxic anoxia of brief duration on the LD 50 and on the radiation syndrome observed in mammals after total body irradiation. It was found that this brief anoxic anoxia produced by irradiating rats in 5 per cent oxygen for approximately eight minutes protected them from otherwise lethal doses of total body irradiation. The thirty day LD 50 for rats irradiated in 5 per cent oxygen appears to be between 1,200 and 1,400 r as contrasted with an LD 50 of slightly higher than 600 r in irradiated control rats.

Histotoxic anoxia produced by intraperitoneal injection of NaCN failed to protect the rats from roentgen irradiation. Thus, it appears that irradiation injury appears to be correlated with the presence or absence of oxygen in tissues.—*E. M. Cooper, M.D.*

Jaeger, Rudolph. Irritating effect of iodized vegetable oils on the brain and spinal cord when divided into small particles. *Arch. Neurol. & Psychiat.*, Nov., 1950, *64*, 715–719.

Emulsified iodized vegetable oils were prepared and injected within the cisterna, spinal subarachnoid space and in some cases the ventricles of dogs. Emulsions were prepared from three standard vegetable oils: (lipiodol; an iodized poppyseed oil), chloriodized oil (iodochloral; an iodized peanut oil), and iodized corn oil. The reason was to produce particles small enough to be absorbed from the subarachnoid space or that at least they could be withdrawn upon completion of the examination. The emulsifying agents were isotonic sodium chloride and powdered acacia. Human and dog blood serums were also used as emulsified materials. It was determined beforehand that these emulsifying agents were non-irritating. A control group was injected with the standard preparation of non-emulsifying iodized oils. Five-tenths cubic centimeter of these agents was injected per 4.5 kg. of body weight. In all animals, including those who did not die, there was an immediate reaction. Some became immediately ill, some became paraplegic. Grossly the lesions were characterized by a severe arachnoiditis, greatest at the site of injection. No area of the subarachnoid space escaped injury. The author has no rational explanation for this severe response other than that it may be due to minute emulsified particles.

In addition, pantopaque was prepared as the above agents, being emulsified and similarly injected. A similar response occurred.—*F. W. O'Brien, Jr., M.D.*

Chapman, W. H., Sipe, C. R., Eltzholtz, D. C., Cronkite, E. P., and Chambers, F. W., Jr. Sulfhydryl-containing agents and the effects of ionizing radiations. I. Beneficial effect of glutathione injection on x-ray induced mortality rate and weight loss in mice. *Radiology*, Dec., 1950, *55*, 865–873.

It has been reported that glutathione has a beneficial effect on roentgen intoxication, hence studies on survival rate in mice following total body irradiation with 800 r (1,000 kv., half-value layer 2.2 mm. lead) were undertaken. The glutathione was administered subcutaneously in a total dose of 60 mg. per 100 gm. of mouse before irradiation and in a total dose of 160 mg. per 100 gm. of mouse divided equally before and after irradiation in well controlled experiments. Survival rate was 63.8 per cent for the glutathione treated mice as compared with 40 to 46 per cent for the controls, which, when treated statistically, gave a probability of less than 0.001. Also, the surviving glutathione treated mice showed less weight loss during the first fourteen days following irradiation and withstood trauma from a Noble-Collip drum to a better degree than the surviving irradiated controls. The slough produced by the injection was eliminated by bringing the pH of the glutathione solution from 2.9 to 6.0. The mechanism of the protective action of glutathione is not known. —*M. B. Goodwin, M.D.*

Eschner, E. G., and Stephenson, B. R. Electronic timer for developing rooms and physiotherapy. *Radiology*, Dec., 1950, *55*, 890–892.

An electronic timer based on the time of discharge of a condenser through a resistor is described, such a timer being used in place of a time interval clock. The thyratron is used as the rectifier as well as a relay control, hence the peak charge is dependent only on the line voltage, thereby minimizing error. The circuit constants used allow for preset times from ten seconds to twenty minutes with good accuracy. When the bell rings, the technician opens the switch and the condenser is immediately recharged preparatory for the next timed interval.—*M. B. Goodwin, M.D.*

H. DABNEY KERR

President of the American Roentgen Ray Society, 1951–1952
Janeway Lecturer, American Radium Society, 1951